Oxycodone for cancer-related pain (Review)

Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 2

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 3
METHODS . . . 3
RESULTS . . . 6
Figure 1. . . . 7
Figure 2. . . . 9
Figure 3. . . . 10
DISCUSSION . . . 13
AUTHORS' CONCLUSIONS . . . 15
ACKNOWLEDGEMENTS . . . 15
REFERENCES . . . 16
CHARACTERISTICS OF STUDIES . . . 20
DATA AND ANALYSES . . . 96
Analysis 1.1. Comparison 1 Pain, Outcome 1 Pain intensity. . . . 97
ADDITIONAL TABLES . . . 98
APPENDICES . . . 111
HISTORY . . . 114
CONTRIBUTIONS OF AUTHORS . . . 115
DECLARATIONS OF INTEREST . . . 115
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 115
NOTES . . . 115

[Intervention Review]

Oxycodone for cancer-related pain

Mia Schmidt-Hansen[1], Michael I Bennett[2], Stephanie Arnold[1], Nathan Bromham[1], Jennifer S Hilgart[1]

[1]National Collaborating Centre for Cancer, Cardiff, UK. [2]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK

Contact address: Mia Schmidt-Hansen, National Collaborating Centre for Cancer, 2nd Floor, Park House, Greyfriars Road, Cardiff, CF10 3AF, UK. Mia.Schmidt-Hansen@wales.nhs.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New, published in Issue 2, 2015.
Review content assessed as up-to-date: 13 March 2014.

Citation: Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS. Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No.: CD003870. DOI: 10.1002/14651858.CD003870.pub5.

ABSTRACT

Background

Many patients with cancer experience moderate to severe pain that requires treatment with strong opioids, of which oxycodone and morphine are examples. Strong opioids are, however, not effective for pain in all patients, nor are they well-tolerated by all patients. The aim of this review was to assess whether oxycodone is associated with better pain relief and tolerability than other analgesic options for patients with cancer pain.

Objectives

To assess the effectiveness and tolerability of oxycodone for pain in adults with cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE and MEDLINE In-Process (Ovid), EMBASE (Ovid), Science Citation Index, Conference Proceedings Citation Index - Science (ISI Web of Science), BIOSIS (ISI), PsycINFO (Ovid) and PubMed to March 2014. We also searched Clinicaltrials.gov, metaRegister of Controlled Trials (mRCT), EU Clinical Trials Register and World Health Organization International Clinical Trials Registry Platform (ICTRP). We checked the bibliographic references of relevant identified studies and contacted the authors of the included studies to find additional trials not identified by the electronic searches. No language, date or publication status restrictions were applied to the search.

Selection criteria

We included randomised controlled trials (parallel-group or cross-over) comparing oxycodone (any formulation or route of administration) with placebo or an active drug (including oxycodone) for cancer background pain in adults.

Data collection and analysis

Two authors independently extracted study data (study design, participant details, interventions and outcomes) and independently assessed the quality of the included studies according to standard Cochrane methodology. Where possible, we meta-analysed the pain intensity data using the generic inverse variance method, otherwise these data were summarised narratively along with the adverse event and patient preference data. The overall quality of the evidence for each outcome was assessed according to the GRADE approach.

Main results

We included 17 studies which enrolled/randomised 1390 patients with 1110 of these analysed for efficacy and 1170 for safety. The studies examined a number of different drug comparisons. Four studies compared controlled release (CR) oxycodone to immediate release (IR) oxycodone and pooled analysis of three of these studies showed that the effects of CR and IR oxycodone on pain intensity after treatment were similar (standardised mean difference (SMD) 0.1, 95% confidence interval (CI) -0.06 to 0.26; low quality evidence). This was in line with the finding that none of the included studies reported differences in pain intensity between the treatment groups. Three of the four studies also found similar results for treatment acceptability and adverse events in the IR and CR groups; but one study reported that, compared to IR oxycodone, CR oxycodone was associated with significantly fewer adverse events.

Six studies compared CR oxycodone to CR morphine and pooled analysis of five of these studies indicated that pain intensity did not differ significantly between the treatments (SMD 0.14, 95% CI -0.04 to 0.32; low quality evidence). There were no marked differences in adverse event rates, treatment acceptability or quality of life ratings.

The remaining seven studies either compared oxycodone in various formulations or compared oxycodone to different alternative opioids. None of them found any clear superiority or inferiority of oxycodone for cancer pain, neither as an analgesic agent nor in terms of adverse event rates and treatment acceptability.

The quality of this evidence base was limited by the risk of bias of the studies and by small sample sizes for many outcomes. Random sequence generation and allocation concealment were under-reported, and the results were substantially compromised by attrition with data missing from more than 20% of the enrolled/randomised patients for efficacy and from more than 15% for safety.

Authors' conclusions

Overall, the data included within this review suggest that oxycodone offers similar levels of pain relief and adverse events to other strong opioids including morphine, which is commonly considered the gold standard strong opioid. Our conclusions are consistent with other recent reviews and suggest that while the reliability of the evidence base is low, given the absence of important differences within this analysis it seems unlikely that larger head to head studies of oxycodone versus morphine will be justified. This means that for clinical purposes oxycodone or morphine can be used as first line oral opioids for relief of cancer pain.

PLAIN LANGUAGE SUMMARY

Oxycodone for cancer-related pain

Many patients with cancer experience moderate to severe pain that requires treatment with strong painkillers that are classified as opioids. Oxycodone and morphine are examples of such strong painkillers that are used for the relief of cancer pain. Strong painkillers are, however, not effective for pain in all patients nor are they well-tolerated by all patients. The aim of this review is to assess whether oxycodone is associated with better pain relief and tolerability than other strong painkillers for patients with cancer pain. We found 17 relevant studies that compared different types of oxycodone to each other or to other strong painkillers. Generally, the studies showed that oxycodone is an equally effective strong painkiller whether taken every 6 or every 12 hours. All the strong painkillers examined in the studies are also associated with a number of unwanted effects, such as vomiting, constipation and drowsiness. Overall, we found that the current evidence base is comprised of studies that contain small numbers of patients of which there is a significant (20%) dropout rate. However, given the absence of important differences within this analysis, it seems unlikely that larger head to head studies of oxycodone versus morphine are justified.

BACKGROUND

Description of the condition

Pain from cancer can be caused by direct invasion of a tumour into soft tissue or bone and is often a presenting symptom at the time of diagnosis of cancer. A European survey published in 2009 found that of 5000 cancer patients (including 617 community-based

National Health Service (NHS) patients in the United Kingdom (UK)) 72% experienced pain (77% of UK patients) which was of moderate to severe intensity in 90% of this group (Breivik 2009). This is consistent with a recent systematic review that demonstrated cancer pain prevalence of up to 75% in advanced disease, and that almost one in two patients are undertreated (Deandrea 2008). Pain in cancer patients may also be caused by cancer treatments and by co-morbid conditions. In this review, we define cancer pain as pain arising as a direct consequence of the cancer, and not from other aetiologies.

Description of the intervention

Oxycodone is a strong opioid analgesic indicated for the treatment of moderate to severe chronic pain, including cancer pain. It is available orally as immediate release solution and tablets (for 4-hourly dosing) and as sustained (controlled) release tablets (for 12-hourly dosing). It is also available as a parenteral injection. In some countries, oxycodone is available as a compound with acetaminophen (paracetamol) or ibuprofen.

How the intervention might work

Oxycodone works primarily as an agonist of mu-opioid receptors in the spinal cord and brain. It has some activity at kappa-opioid receptors (which are also involved in nociception or analgesia) though the importance of this mechanism in the overall analgesic effect of oxycodone is unclear. Despite animal studies suggesting differences in pharmacodynamics, these have not been demonstrated in clinical studies to date. Therefore, the shared mechanism of action to other strong opioids (that is agonist activity at mu-opioid receptors) means that clinical benefits and adverse effects are likely to be similar. However, important differences exist in the pharmacokinetics of strong opioids (for example morphine undergoes second phase elimination via glucuronidation, while oxycodone undergoes extensive first phase metabolism via CYP2D6 and CYP3A4 pathways) so clinical equivalence cannot be inferred (Gudin 2012; Leppert 2010).

Why it is important to do this review

The World Health Organization published the Method for Cancer Pain Relief (WHO analgesic ladder) in 1986 (WHO 1986) which advocates a stepwise approach to analgesia for cancer pain and revolutionised the use of oral opioids. It recommended that morphine be used first line for moderate to severe cancer pain. Observational studies have suggested that this approach results in pain control for 73% of patients (Bennett 2008) with a mean reduction in pain intensity of 65% (Ventafridda 1987).

Many patients with cancer experience moderate to severe pain that requires treatment with strong analgesics. Oxycodone and morphine are examples of strong opioids that are used for the relief of cancer pain. Strong opioids are, however, not effective for pain in all patients, nor are they well-tolerated by all patients. Recent guidance by the European Association for Palliative Care on the use of opioids in cancer pain suggests that oxycodone could be used as first line treatment of moderate to severe cancer pain as an alternative to morphine (Caraceni 2012). The aim of this review is to assess whether oxycodone is associated with better pain relief and tolerability than other analgesic options for patients with cancer. The protocol for this review was updated from Reid 2010.

OBJECTIVES

To assess the effectiveness and tolerability of oxycodone for pain in adults with cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), with parallel-group or crossover design, comparing oxycodone (any formulation and any route of administration) with placebo or an active drug (including oxycodone) for cancer background pain. We did not examine studies on breakthrough pain.

Types of participants

Adults (aged $\geq$ 18 years) with cancer pain.

Types of interventions

Oxycodone (any dose, formulation and route of administration) versus oxycodone (any dose, formulation and route of administration)

Oxycodone (any dose, formulation and route of administration) versus other active drug (any dose, formulation and route of administration)

Oxycodone (any dose, formulation and route of administration) versus placebo

Types of outcome measures

Primary outcomes

Pain intensity and pain relief.
Both of these outcomes had to be patient-reported and could be reported in any transparent manner (for example by using numerical or verbal rating scales). We did not consider these outcomes when reported by physicians, nurses or carers. If possible, we aimed to distinguish between nociceptive and neuropathic pain, but the data were not presented in a manner that made this possible.

Secondary outcomes

Side effects or adverse events (e.g., constipation, nausea, vomiting, drowsiness, confusion, respiratory depression), quality of life and patient preference.
We considered all of these outcomes as they were reported in the included studies.

Search methods for identification of studies

We did not apply language, date or publication status (published in full, published as abstract, unpublished) restrictions to the search.

Electronic searches

We identified relevant trials by searching the following databases:
1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 1 of 12, 2014);
2. MEDLINE and MEDLINE In-Process (Ovid) (1946 to 3 March 2014);
3. EMBASE (Ovid) (1947 to March 2014);
4. Science Citation Index (Web of Science) (1899 to 3 March 2014);
5. Conference Proceedings Citation Index - Science (Web of Science) (1990 to 3 March 2014);
6. BIOSIS (Web of Science) (1926 to 3 March 2014);
7. PsycINFO (Ovid) (1806 to February week 4 2014);
8. PubMed (to 3 March 2014).

We applied to this search the Cochrane highly sensitive search strategy for identifying randomised control trials (Lefebvre 2011). The search strategies used can be found in Appendix 1.

Searching other resources

We checked the bibliographic references of relevant identified studies in order to find additional trials not identified by the electronic searches. We also searched Clinicaltrials.gov (13 March 2014), metaRegister of Controlled Trials (mRCT) (3 March 2014), EU Clinical Trials Register (3 March 2014) and World Health Organization International Clinical Trials Registry Platform (ICTRP) (3 March 2014) as complementary sources for related studies, and we contacted authors of the included studies to ask if they knew of any other relevant studies.

Data collection and analysis

Selection of studies

Two of the review authors (MSH, NB) assessed the titles and abstracts of all the studies identified by the search for potential inclusion. We independently considered the full records of all potentially relevant studies for inclusion by applying the selection criteria outlined in the Criteria for considering studies for this review section. We resolved any disagreements by discussion. We did not restrict the inclusion criteria by date, language or publication status (published in full, published as abstract, unpublished).

Data extraction and management

Using a standardised data extraction form, two authors (MSH, JSH) extracted data pertaining to study design, participant details (including age, cancer characteristics, previous analgesic medication and setting), interventions (including details about titration) and outcomes. We resolved any disagreements by discussion. If there were studies for which only a subgroup of the participants met the inclusion criteria for the current review, we would only extract data on this subgroup provided randomisation had not been broken, however, no such studies were identified for inclusion.

Assessment of risk of bias in included studies

Two of the authors (MSH, JSH) independently assessed the methodological quality of each of the included studies by using the 'risk of bias' assessment method outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For each study we assessed the risk of bias for the following domains: selection bias (study level; 2 items; random sequence generation, allocation concealment), performance bias (outcome level; 2 items; blinding of patients, blinding of treating personnel), detection bias (outcome level; 1 item; blinding of outcome assessment), attrition bias (outcome level; 1 item; incomplete outcome data) and reporting bias (study level; 1 item; selective reporting). We also included an item that assessed the adequacy of titration (with judgements made based on any available relevant information, including design features, inclusion criteria, and interim pain assessments) and another item that captured whether data were available for both time periods in cross-over trials. Each of the 'risk of bias' items required a 'low risk', 'high risk' or 'unclear risk' response. We also documented the reasons for each response in accordance with Higgins 2011, and resolved any disagreements on the 'risk of bias' ratings through discussion.

The GRADE approach was used to assess the overall quality of the evidence for each outcome, with downgrading of the evidence from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias (Lagendam 2013). We included the following outcomes in the summary of findings table (Table 1): pain intensity, adverse events, treatment acceptability and quality of life.

Measures of treatment effect

For pain intensity we extracted the means and standard deviations and we used these to estimate the standardised mean difference (SMD) between the treatments along with the 95% confidence interval (CI), as the outcome was not measured on the same scale across studies. For adverse events we extracted event rates with the aim of calculating risk ratios, however inspection of the data indicated that this was not feasible.

Unit of analysis issues

The patient was the unit of analysis, but in a number of cases the data reported in the included cross-over trials could not otherwise be incorporated into the analyses (see Dealing with missing data), so we included them as if the design had been parallel-group. Higgins 2011 (in chapter 16) points out that this approach, while giving rise to unit of analysis error, is nevertheless conservative as it results in an under-weighting of the data. We had planned to perform sensitivity analyses assessing the impact of this strategy if we included cross-over trial data in this manner, but we were unable to perform such analyses due to the low number of included studies in the meta-analyses.

Dealing with missing data

In cases where data were missing, we contacted the authors to request the missing data. This strategy did not result in any additional data. We planned to limit imputation of missing data to the imputation of missing standard deviations, if enough information was available from the studies to calculate the standard deviation according to the methods outlined by Higgins 2011. This was not the case, so no data were imputed. We recorded the dropout/missing data rates in the 'risk of bias' tables under the items on attrition bias and in the 'Participants' section of the Characteristics of included studies, and we addressed the potential effect of the missing data on the results in the 'Discussion' section of the review. It was not possible to assess the impact of missing data in sensitivity analyses due to the low study number. In all cases we aimed to perform intention-to-treat analyses.

Assessment of heterogeneity

We assessed heterogeneity by using the I^2 statistic. We considered I^2 values above 50% to represent substantial heterogeneity in line with Higgins 2011 and we planned to assess potential sources of heterogeneity through subgroup analyses as outlined in Subgroup analysis and investigation of heterogeneity.

Assessment of reporting biases

In addition to implementing the comprehensive search strategy outlined in the section Search methods for identification of studies, the risk of outcome reporting bias was illustrated in the 'Risk of bias' summary figures that we constructed for each study and each type of assessed bias.

Data synthesis

We entered the data extracted from the included studies into Review Manager (RevMan 2014), which was used for data synthesis. We analysed pain intensity using the generic inverse variance method in accordance with Higgins 2011. As I^2 was not above 50% we used a fixed-effect model. However, given the limitations of this analysis strategy as outlined in the Unit of analysis issues section, we also considered the results of the individual studies. We planned to meta-analyse the adverse events data by using the Mantel-Haenszel method, however, due to the generally low number of studies and the variability in the reporting of the adverse events as well as in study design within each comparison it was not feasible to meta-analyse the adverse events data. Adverse events were instead summarised narratively and in tables.

Subgroup analysis and investigation of heterogeneity

Different aspects of the trials are likely to contribute heterogeneity to the proposed main analyses. If there were sufficient data, we therefore planned to perform subgroup analyses based on doses, titration, formulations (for example immediate-release, sustained-release), routes of administration (for example oral, rectal), length of the trials and populations (for example adults, opioid-naive patients). However, as there were not sufficient data, we were unable to perform any subgroup analyses.

Sensitivity analysis

If sufficient data were available, we planned to examine the robustness of the meta-analyses by conducting sensitivity analyses using different components of the 'risk of bias' assessment, particularly those relating to whether allocation concealment and blinding were adequate. We also planned to conduct further sensitivity analyses to examine the impact of missing data on the results if a large proportion of the studies were at an 'unknown' or 'high risk' of attrition bias and, finally, we planned to use sensitivity analyses

to examine whether publication status and trial size influenced the results. Unfortunately, we were unable to perform any sensitivity analyses due to the low number of studies within each comparison.

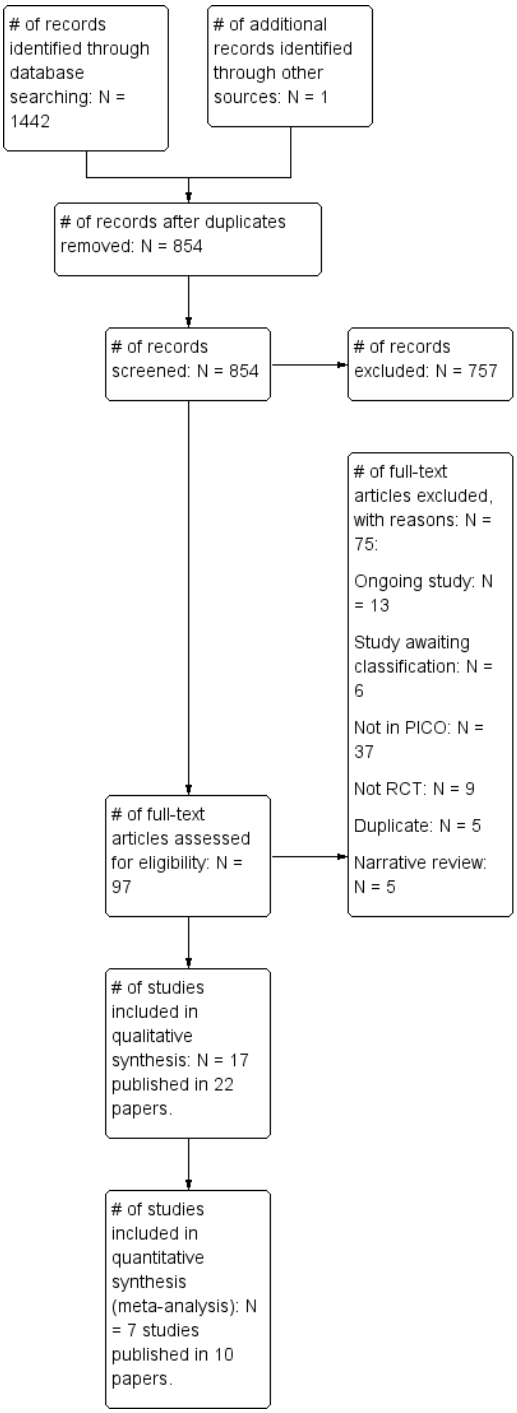
RESULTS

Description of studies

Results of the search

The search identified 854 unique records of which 757 were excluded based on the title/abstract and 97 were retrieved for full-text evaluation. Of the 97 records, 17 studies published in 22 articles were included, while 56 were excluded because they were: not conducted in the target population examining the target comparisons as measured by the target outcomes of this review (not following the PICO of this review) (N = 37), not RCTs (N = 9), narrative reviews (N = 5) or duplicates (N = 5). See also Figure 1. In addition to the 17 included studies, 13 ongoing studies and 6 potentially relevant studies were identified by the search. One of the ongoing studies was published in full after the search but before publication of this review. This study was therefore also included. We await further information, including study completion and publication, of the six potentially relevant studies before we can ascertain their relevance to the current review and classify them accordingly. See Characteristics of ongoing studies and Characteristics of studies awaiting classification, respectively.

Figure 1. Study flow diagram.



Included studies

The 17 included studies enrolled/randomised a total of 1390 patients (651 males, 621 females; for the remaining 118 patients gender was not specified) with 1110 of these analysed for efficacy and 1170 for safety. The reported mean/median ages of the patient populations in the studies ranged from 45 years to 68.8 years. Ten of the studies were cross-over trials (Beaver 1978; Beaver 1978a; Bruera 1998; Gabrail 2004; Hagen 1997; Heiskanen 1997; Kalso 1990; Lauretti 2003; Leow 1995; Stambaugh 2001) and seven were parallel-group trials (Imanaka 2013; Kaplan 1998; Mercadante 2010; Mucci-LoRusso 1998; Parris 1998; Riley 2014; Salzman 1999), with eight of the studies conducted in the USA (Beaver 1978; Beaver 1978a; Gabrail 2004; Kaplan 1998; Mucci-LoRusso 1998; Parris 1998; Salzman 1999; Stambaugh 2001), two in Canada (Bruera 1998; Hagen 1997), two in Finland (Heiskanen 1997; Kalso 1990) and one each in Italy (Mercadante 2010), Australia (Leow 1995), Brazil (Lauretti 2003), the UK (Riley 2014) and Japan/Korea (Imanaka 2013). The length of the trials ranged from single dose treatment to one year, and the studies reported the following comparisons:

- controlled-release (CR) oxycodone versus immediate-release (IR) oxycodone (Kaplan 1998; Parris 1998; Salzman 1999; Stambaugh 2001);
- CR oxycodone versus CR morphine (Bruera 1998; Heiskanen 1997; Lauretti 2003; Mercadante 2010; Mucci-LoRusso 1998; Riley 2014);
- CR oxycodone versus CR hydromorphone (Hagen 1997);
- CR oxycodone versus extended-release (ER) oxymorphone (Gabrail 2004);
- CR oxycodone versus ER tapentadol (Imanaka 2013);
- intravenous (IV) oxycodone versus rectal oxycodone (Leow 1995);
- IV oxycodone followed by IR oxycodone versus IV morphine followed by IR morphine (Kalso 1990);
- intramuscular (IM) oxycodone versus oral oxycodone (Beaver 1978);
- IM oxycodone versus IM morphine versus IM codeine (Beaver 1978a).

See also Characteristics of included studies for further details about the studies.

Excluded studies

A number of the studies identified in the search compared oxycodone in combination with another drug (for example naxolone or acetaminophen) against oxycodone alone or placebo. Such studies were not included as they would not answer our primary question, which concerned the effectiveness of oxycodone for cancer pain. See also Characteristics of excluded studies.

Risk of bias in included studies

The risk of bias for the included studies is described in this section. See also Figure 2 and Figure 3 for summaries of the risk of bias judgements made for the included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

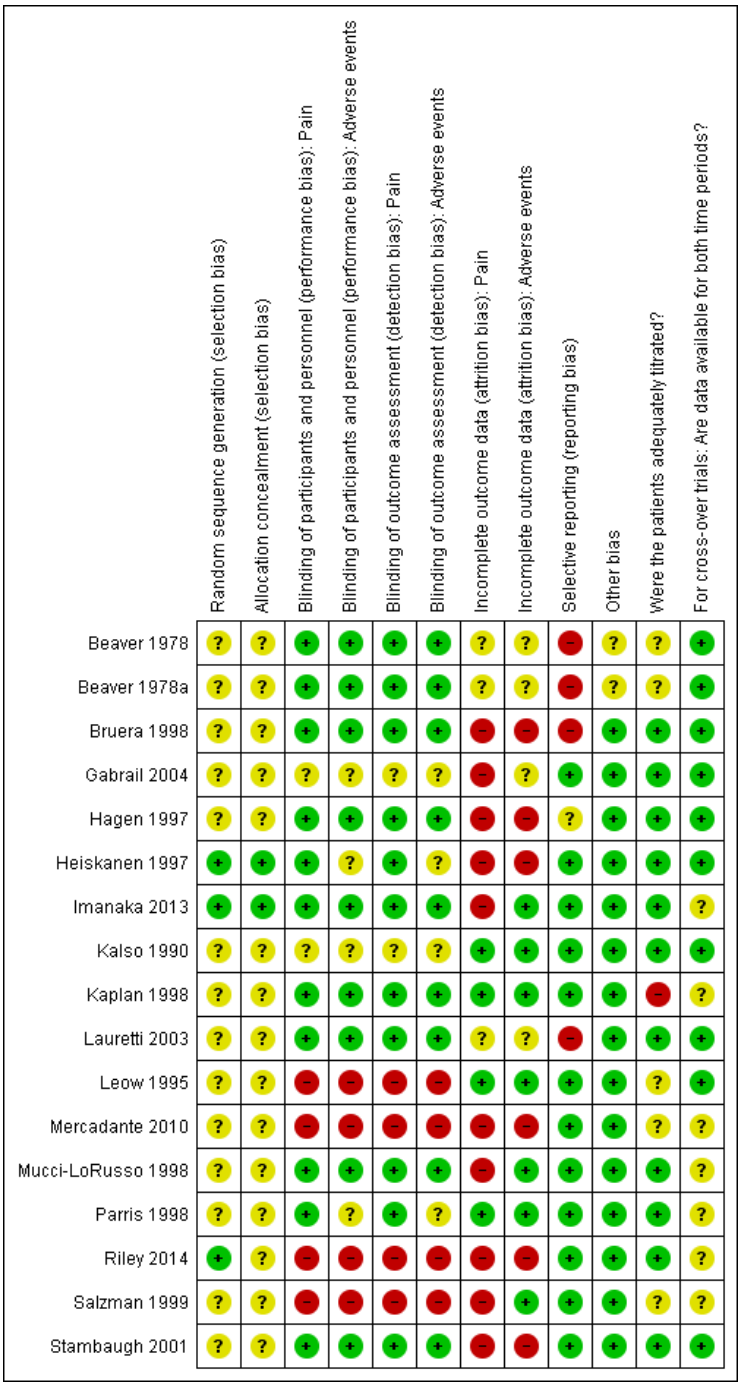
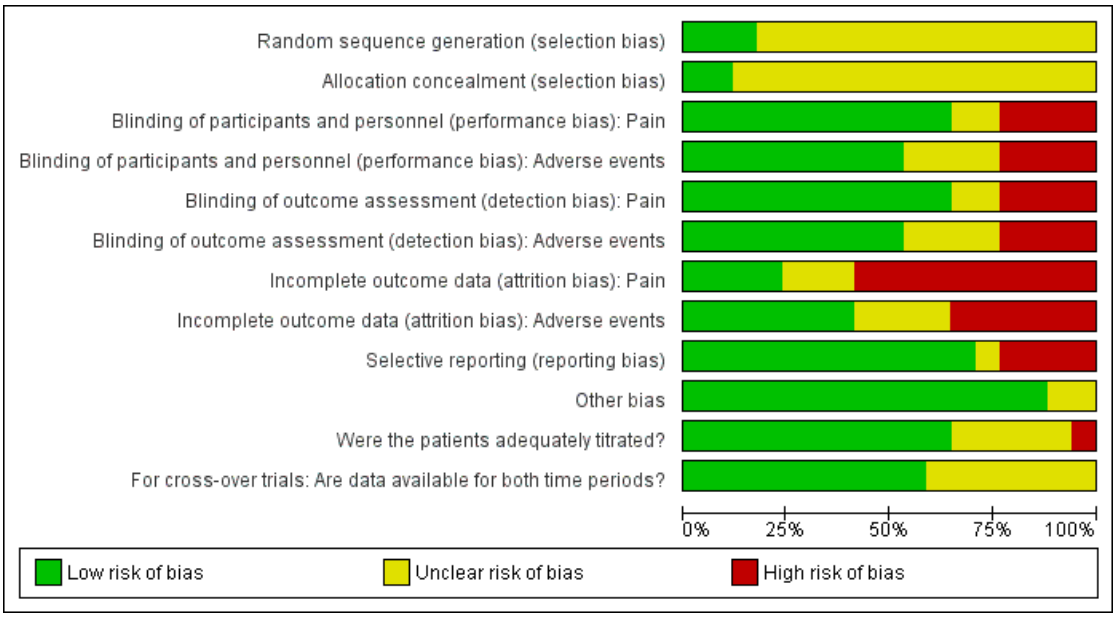


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

In all but three studies, not enough information was reported to assess whether the methods employed to generate the randomisation sequence and to ensure allocation concealment were adequate. Two of these studies were considered to be at low risk of bias for both items (Heiskanen 1997; Imanaka 2013), while the third study was considered at low risk of bias for randomisation sequence but at unclear risk of bias for allocation concealment (Riley 2014). Only four studies reported enough information for us to make a judgement that the treatment groups were comparable at baseline (Imanaka 2013; Kaplan 1998; Riley 2014; Salzman 1999). In the remaining studies, it was unclear whether the patient selection methods employed had resulted in comparable, balanced groups at the start of the study.

Blinding

The problem of under-reporting was also an issue when assigning risk of bias estimates to the items assessing performance and detection bias, that is, blinding. In no instance was it directly and unequivocally reported who was blinded, so we had to infer, on the basis of supplementary information, whether we were reasonably certain that blinding had been adequately executed for a given individual (that is patient, treating personnel and/or the outcome assessors, where not the patients themselves). On this basis, the risk of performance bias was considered to be low for the primary outcome of pain in 11 of the studies (Beaver 1978; Beaver 1978a; Bruera 1998; Hagen 1997; Heiskanen 1997; Imanaka 2013; Kaplan 1998; Lauretti 2003; Mucci-LoRusso 1998; Parris 1998; Stambaugh 2001), unclear in two studies (Gabrail 2004; Kalso 1990) and high in four of the studies that were all described as open-label (Leow 1995; Mercadante 2010; Riley 2014; Salzman 1999). For adverse events, the risk of performance bias was low in nine studies (Beaver 1978; Beaver 1978a; Bruera 1998; Hagen 1997; Imanaka 2013; Kaplan 1998; Lauretti 2003; Mucci-LoRusso 1998; Stambaugh 2001), unclear in four studies (Gabrail 2004; Heiskanen 1997; Kalso 1990; Parris 1998) and high in the same four open-label studies as was the case for pain (Leow 1995; Mercadante 2010; Riley 2014; Salzman 1999). The pattern of judgements was identical for detection bias, for both outcomes. This was the case for the primary outcome of pain because, according to our criteria, this outcome had to be patient reported. It was therefore at risk of detection bias to the same ex-

tent that it was at risk of performance bias since both depend on patient blinding. As is also evident from the bias judgements (see Characteristics of included studies), when a study was described as double-blind but did not describe who was blinded, additional information in the studies generally led us to the conclusion that at least the patients seemed to be blinded, although we did not feel able to gauge with sufficient confidence who else might have been blinded. Given that it was not always clear who assessed the adverse events, this accounts for the similar judgements for performance and detection bias for this outcome.

Incomplete outcome data

Overall the data from only 79.9% of the total number of enrolled/randomised patients were analysed for pain and 84.2% for adverse events, which indicates that attrition bias was a substantial problem in this data set, with only four studies considered at low risk (Kalso 1990; Kaplan 1998; Leow 1995; Parris 1998) and 10 studies considered at high risk (Bruera 1998; Gabrail 2004; Hagen 1997; Heiskanen 1997; Imanaka 2013; Mercadante 2010; Mucci-LoRusso 1998; Riley 2014; Salzman 1999; Stambaugh 2001), while three studies were at unclear risk (Beaver 1978; Beaver 1978a; Lauretti 2003) for the primary outcome of pain. For adverse events, the risk of attrition bias was slightly less with seven studies considered at low risk (Kalso 1990; Kaplan 1998; Imanaka 2013; Leow 1995; Mucci-LoRusso 1998; Parris 1998; Salzman 1999) and six studies considered at high risk (Bruera 1998; Hagen 1997; Heiskanen 1997; Mercadante 2010; Riley 2014; Stambaugh 2001), while four studies were at unclear risk (Beaver 1978; Beaver 1978a; Gabrail 2004; Lauretti 2003).

Selective reporting

Twelve of the included studies were not considered to be at risk of selective reporting bias, whereas four of the studies either did not report adverse events or did not report them in a manner so they could be scrutinised for (and potentially included in) an evidence synthesis (Beaver 1978; Beaver 1978a; Bruera 1998; Lauretti 2003); these studies were therefore judged at high risk. One study only reported four adverse events in a transparent manner and was therefore considered at unclear risk of reporting bias (Hagen 1997).

Other potential sources of bias

The patients appeared to be adequately titrated in the majority of the studies (Bruera 1998; Gabrail 2004; Hagen 1997; Heiskanen 1997; Imanaka 2013; Kalso 1990; Lauretti 2003; Mucci-LoRusso 1998; Parris 1998; Riley 2014; Stambaugh 2001), although this was unclear in four studies (Beaver 1978; Beaver 1978a; Leow 1995; Mercadante 2010) and not the case in one study (Kaplan 1998). One study examined titration as its main objective (Salzman 1999). For all 10 cross-over trials, data were available for all cross-over phases. Only three studies undertook intention-to-treat (ITT) analyses for both efficacy and safety (Leow 1995; Parris 1998; Stambaugh 2001), with a further three studies performing these analyses for safety only (Kalso 1990; Salzman 1999) or for efficacy only (Riley 2014). The remaining studies did not perform ITT for any of the outcomes. The vast majority of the included studies had received commercial funding or had authors who were employees of the drug manufacturers, or both (Beaver 1978; Beaver 1978a; Gabrail 2004; Hagen 1997; Heiskanen 1997; Imanaka 2013; Kaplan 1998; Leow 1995; Mucci-LoRusso 1998; Parris 1998; Salzman 1999; Stambaugh 2001). Only two studies were considered free from the potential influence of commercial funding (Kalso 1990; Riley 2014) with a further three studies having unclear status (Bruera 1998; Lauretti 2003; Mercadante 2010). All the included studies were considered at low risk of any other biases (for example carry-over effects in the cross-over trials) with the exception of two studies which were judged to be at 'unclear risk of other bias' due to the manner in which the trials were reported (Beaver 1978; Beaver 1978a).

Effects of interventions

Analysis 1.1 shows the pain intensity scores for each of the listed treatment groups, subgrouped according to overall treatment comparisons. We felt that presenting the pain intensity data this way for the studies where it was possible gave a comprehensive overview of the pain intensity data for the majority of the included studies, although the actual analyses should be treated with some caution as outlined in the Unit of analysis issues section.

Controlled-release (CR) oxycodone versus immediate-release (IR) oxycodone

Pooled analysis showed that there was no statistically significant difference in pain intensity after treatment with either CR or IR oxycodone (SMD 0.1, 95% CI -0.06 to 0.26) (Analysis 1.1), which was also in line with the finding that none of the included studies reported that the pain intensity differed between the treatment groups. Salzman 1999 could not be included in the pooled analysis due to the design of the study, so is instead summarised narratively below.

Kaplan 1998 reported in a parallel-group study lasting six days that compared to IR oxycodone, CR oxycodone was associated with significantly fewer adverse events overall and adverse events related to the digestive system, and that significantly fewer patients in the CR oxycodone group reported headache compared to the IR oxycodone patients (see also Table 2). Kaplan found no difference in treatment acceptability between the study groups (mean at study end 3.2, SE = 0.1, in both groups).

In a parallel-group trial lasting five days, Parris 1998 reported that all the adverse events observed during the study resolved and the study found no significant differences in incidence rates of adverse

events (see also Table 2) or acceptability of treatment between the study groups.

Stambaugh 2001 conducted a cross-over study with a duration of three to seven days per phase, and stated that: "The study showed similar incidences and numbers of reports of individual adverse events considered related to the IR and CR drug" (page 505), but did not report any formal statistical comparisons of the adverse event rates between the study groups (see also Table 2). In this study 30/30 and 29/30 patients rated IR and CR oxycodone, respectively, as of 'fair', 'good' or 'excellent' acceptability during the last 24 hours of the treatment phases, with 24/30 and 22/30 patients rating the drugs 'good' or 'excellent', respectively.

Salzman 1999 examined in a parallel-group trial lasting up to 21 days whether CR oxycodone could be used as readily as IR oxycodone for titration to stable pain control and found that 22/24 and 19/24 patients in the CR and IR groups, respectively, achieved stable pain control within a mean time of 1.6 days (SE = 0.4) and 1.7 days (SE = 0.6), respectively, with no significant differences in the incidence of adverse events between the groups (see also Table 2).

CR oxycodone versus CR morphine

Pooled analysis including Bruera 1998, Heiskanen 1997, Mercadante 2010, Mucci-LoRusso 1998 and Riley 2014 showed that the pain intensity scores after treatment with CR oxycodone and CR morphine did not differ significantly (SMD 0.14, 95% CI -0.04 to 0.32) (Analysis 1.1). Lauretti 2003 could not be included in the pooled analysis due to the design of the study and the results of this study are therefore summarised narratively below.

In a cross-over trial with each phase lasting 7 days, Bruera 1998 reported that 8/23 patients preferred CR oxycodone treatment while 11/23 patients preferred treatment with CR morphine (non-significant difference) and that: "There were no statistically significant differences by treatment in mean severity for any of the elicited adverse events or in the frequency of reporting of unelicited events" (page 3225), but only data on the sedation and nausea visual analogue scale (VAS) ratings were presented (see also Table 3).

Heiskanen 1997 conducted a cross-over trial lasting three to six days per phase and found that vomiting was significantly more common during morphine treatment while constipation was significantly more common during oxycodone treatment; and reported no other significant differences in adverse event rates between the drugs (see also Table 3). However, the mean daily acceptability of treatment ratings were significantly higher for morphine (3.49/5; SE = 0.12) than for oxycodone (3.19/5; SE = 0.11).

In a parallel-group trial lasting four weeks (with an extension of another four weeks), Mercadante 2010 found no significant differences in the reported adverse events between the groups.

Mucci-LoRusso 1998 conducted a parallel-group trial lasting up to 12 days and found that 40/48 and 42/52 patients achieved stable pain control after receiving CR oxycodone and CR morphine, respectively, within a median of 2 days for both groups (ranges were 1 to 10 and 1 to 9 days, respectively). Mucci-LoRusso 1998 also found that 74% and 77% of the CR oxycodone and CR morphine patients, respectively, rated the acceptability of treatment as good to excellent (non-significant) and that the mean acceptability ratings at the study end did not differ significantly between the CR oxycodone (mean 4, SE = 0.1) and CR morphine (mean 3.9, SE = 0.1) patients. The authors also reported that: "Overall, the adverse experience profiles of CR oxycodone and CR morphine were similar" (page 244; see also Table 3) and that there were no clinically significant changes in quality of life for either treatment group, although no formal analyses were shown for the former and no results or analyses were shown for the latter outcome.

Lauretti 2003 conducted a two-phase (each lasting 14 days) cross-over study to examine IR morphine consumption (which was the main outcome) during treatment with CR oxycodone and CR morphine, keeping the ratio of CR oxycodone and CR morphine constant (1:1.8). IR morphine was used as rescue medication and the patients were allowed to take as much as necessary to keep VAS pain below 4. The patients consumed 38% more IR morphine during treatment with CR morphine than with CR oxycodone. Lauretti also found that CR and IR morphine were associated with more nausea and vomiting (see also Table 3) and a similar acceptance to the study drugs compared to the combination of CR oxycodone and IR morphine. Lauretti 2003 concluded that the results indicated that CR oxycodone combined with IR morphine was associated with superior analgesia and lower, or similar, rates of adverse events than a combination of CR and IR morphine.

In an open-label, parallel-group trial of 1-year duration, Riley 2014 compared CR oxycodone (N = 100) to CR morphine (N = 98) and found that 67% and 62% of the patients achieved a response to first line oxycodone and morphine, respectively, and that this was not a significant difference. Moreover, in the patients who achieved a response to their assigned first line treatment none of the five pain indices studied (that is 'worst pain', 'least pain', 'average pain', 'pain right now', and 'percentage relief') differed significantly between the treatment groups. The authors also found no significant differences in adverse event reaction scores between oxycodone and morphine, either in first line responders or non-responders. The adverse event rates are listed in Table 3.

CR oxycodone versus CR hydromorphone

In a cross-over trial lasting seven days per phase, Hagen 1997 found no difference in pain intensity between treatment with CR oxycodone and CR hydromorphone (see also Analysis 1.1). Hagen 1997 also reported that no differences in the frequency of adverse events were observed between the treatment groups with the exception of drowsiness, which occurred more during treatment with oxycodone (see also Table 4); 25.8% of the patients had no treatment preference with approximately half of the remaining pa-

tients preferring oxycodone (35.5%) while the other half preferred hydromorphone (38.7%).

CR oxycodone versus extended-release (ER) oxymorphone

Gabrail 2004, in a cross-over trial with each phase lasting 7 to 10 days, found clinically indistinguishable mean 24-hour average daily pain intensity ratings and also reported that no differences were observed in quality of life (general activity, mood, walking ability, normal work, relationships with others, sleep and enjoyment of life) between the drugs, and that 78.3% of patients rated oxycodone as 'excellent', 'very good' or 'good' with 86.4% of the patients giving oxymorphone such ratings. The adverse event rates were also reported to be similar between the drug comparisons, although no formal statistical analyses were presented (see also Table 4), and no patients withdrew due to abnormal laboratory values, insufficient analgesia or loss to follow-up.

CR oxycodone versus ER tapentadol

Imanaka 2013, in a parallel-group trial of 4 weeks duration, found equal analgesia between the study groups (see also Analysis 1.1) with 82/139 oxycodone patients and 80/126 tapentadol patients reporting ≥ 30% improvement in pain intensity during the last 3 days of treatment, and 59/139 oxycodone patients and 63/126 tapentadol patients reporting ≥ 50% improvement in pain intensity during the last 3 days of treatment. Inspection of Table 4 suggests that the adverse events rates were comparable between the treatment groups, but the authors did not present any formal statistical analyses of this apparent equality.

Intravenous (IV) oxycodone versus rectal oxycodone

Leow 1995 conducted a single-dose cross-over study in 12 patients, with each phase lasting 24 hours, and found that while IV oxycodone was associated with faster onset of pain relief relative to rectal oxycodone, rectal oxycodone was associated with a longer duration of pain relief compared to IV oxycodone. Leow 1995 reported no significant differences in the side effect profiles for the two study arms (see also Table 4).

IV oxycodone followed by IR oxycodone versus IV morphine followed by IR morphine

In a cross-over study comparing IV oxycodone titration (2 days) followed by IR oxycodone titration (2 days) with IV morphine titration (2 days) followed by IR morphine titration (2 days) in 19 analysed patients Kalso 1990 found that the patients achieved equal analgesia with both drugs, but around 30% more IV oxycodone was needed compared to IV morphine and around 25% less IR oxycodone was needed than IR morphine to achieve this. Kalso 1990 also found that nausea was significantly more common with oral morphine treatment compared to the other three treatment modalities (see also Table 4). Ten patients expressed no treatment preference while five patients preferred oxycodone while another five patients preferred treatment with morphine.

Intramuscular (IM) oxycodone versus oral oxycodone

In a single-dose, cross-over study Beaver 1978 compared 5 and 15 mg IM oxycodone to 10 and 30 mg oral oxycodone in 17 patients of whom 13 completed at least one cross-over round of the study medications. Beaver 1978 reported that oral oxycodone was 0.57 (95% CI 0.22 to 1.84) times as potent as IM oxycodone for pain relief and 0.78 (95% CI 0.3 to 8.82) times as potent for change in pain intensity. The side effects for both oral and IM oxycodone, although infrequent, were related to dose, but otherwise no further details on the observed side effects were provided.

IM oxycodone versus IM morphine versus IM codeine

In another single-dose, cross-over study Beaver 1978a compared 7.5 mg, 15 mg and 30 mg IM oxycodone to 8 mg, 16 mg and 32 mg IM morphine in 34 patients of whom 28 completed at least one round of the study drugs. In this study, IM oxycodone was found to be 0.74 (95% CI 0.36 to 1.2) times as potent as IM morphine for pain relief and 0.68 (95% CI 0.32 to 1.07) times as potent as IM morphine for change in pain intensity. In a further study of similar design Beaver 1978a compared 7.5 mg, 15 mg and 30 mg IM oxycodone to 90 mg and 180 mg IM codeine and to 16 mg IM morphine in 30 patients of whom 26 completed at least one cross-over round of the study medications. Beaver 1978a reported that IM oxycodone was 10.72 (95% CI not reported) times as potent as IM codeine for pain relief and 8.44 (95% CI 2.13 to 44.69) times as potent as IM codeine for change in pain intensity. The authors noted that in both studies side effects typical of narcotic analgesics were observed, although not in sufficient numbers to allow meaningful analysis, and they reported no further details on adverse events.

DISCUSSION

Summary of main results

We included 17 studies which enrolled/randomised a total of 1390 patients, with 1110 of these analysed for efficacy and 1170 for safety. The studies examined a number of different drug comparisons. Four studies compared controlled-release (CR) oxycodone to immediate-release (IR) oxycodone, and pooled analysis of three of these studies showed that there was no difference in pain intensity after treatment with either CR or IR oxycodone (SMD 0.1, 95% CI -0.06 to 0.26), which is also in line with the finding that

none of the included studies reported that the pain intensity differed between the treatment groups. Three of the four studies also found no difference in treatment acceptability or adverse events between the comparisons, but one study did report that compared to IR oxycodone, CR oxycodone was associated with significantly fewer adverse events. We noted that IR oxycodone was given every six hours rather than every four hours in these studies. This might have biased the efficacy data in favour of CR oxycodone, however, the adverse effect data suggest that giving IR oxycodone every four hours (more frequently) would have resulted in greater adverse effects, which would have mitigated advantages in efficacy.

Six studies compared CR oxycodone to CR morphine and pooled analysis of five of these six studies indicated that pain intensity did not differ significantly between the treatments (SMD 0.14, 95% CI -0.04 to 0.32) with no marked differences in terms of adverse event rates, treatment acceptability or quality of life ratings between the treatments. These findings, however, contrast somewhat with those reported in Lauretti 2003, which was different in design to the other four studies and examined IR morphine consumption during treatment with CR oxycodone and CR morphine while keeping the ratio of CR oxycodone and CR morphine constant. Lauretti 2003 found that the patients consumed 38% more IR morphine during treatment with CR morphine than with CR oxycodone, and that CR and IR morphine was associated with more nausea and vomiting and a similar acceptance to the study drugs compared to the combination of CR oxycodone and IR morphine, and therefore concluded that CR oxycodone combined with IR morphine is associated with superior analgesia and lower or similar rates of adverse events than a combination of CR and IR morphine.

The remaining seven studies all compared either oxycodone in different formulations or oxycodone to different alternative opioids and none of them found any clear superiority or inferiority of oxycodone for cancer pain, neither as an analgesic agent nor in terms of adverse event rates or treatment acceptability. See also Table 1 for a summary of the findings.

Overall completeness and applicability of evidence

Although the findings of this review are applicable to the population and comparisons defined for this review, that is patients who need treatment with strong opioids for cancer pain, they should be taken in the context that this review found 17 studies that were eligible for inclusion and these studies reported on nine different comparisons involving oxycodone and included only 1390 patients. Moreover, for some of the outcomes (patient satisfaction and quality of life) extremely few data were available. To somewhat mitigate this shortfall, we reported treatment acceptability as a proxy. However, that does not change the fact that the evidence base for the effectiveness and tolerability of oxycodone (relative or absolute) for pain in adults with cancer is very limited and it did not allow us to examine the effectiveness and tolerability of oxycodone in detail through patient or treatment subgroup analyses, or the robustness of the findings in sensitivity analyses. The current evidence base would therefore benefit from more well-designed, large randomised controlled trials.

Quality of the evidence

The quality of the evidence for all the outcomes was low or very low. This is due to imprecision (low patient numbers) in some cases and very serious study limitations in all cases. In general, the assessment of the quality of the included studies was limited by a great extent of under-reporting in the studies, especially for the patient selection items (random sequence generation and allocation concealment), while blinding appeared to be reasonably well undertaken overall, both in terms of treatment performance and outcome assessment. However, as is not unusual for pain research, the results were substantially compromised by attrition, with data missing from more than 20% of the enrolled/randomised patients for efficacy, and from more than 15% for safety. These are substantial proportions and, while it did not appear to be selective attrition, the results must be interpreted with caution.

Potential biases in the review process

We undertook the review according to the methods specified in our protocol, which were all in line with the recommendations of The Cochrane Collaboration as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and included a thorough search strategy designed to maximise the chances of identifying all relevant studies. Contacting authors resulted in no additional studies being identified, that is the review therefore only contains data from published studies, some of which have not reported all the outcome data despite having apparently collected these data. The review may therefore be at some risk of publication bias, although publication bias is usually associated with positive results, and the majority of the included studies did not find significant differences between their treatment groups in terms of efficacy and safety. Moreover, the meta-analyses we undertook included data from cross-over studies that were analysed as if they were parallel-group studies. As outlined in Unit of analysis issues, such practice results in unit of analysis error although, in turn, this leads to an under-weighting rather than over-weighting of the data. In future updates of this review we hope to be able to include enough new studies in the meta-analyses to be able to examine the effect of including cross-over trials in this manner through sensitivity analyses.

Agreements and disagreements with other studies or reviews

King 2011 conducted a systematic review without meta-analysis that also included observational studies and concluded that, "There is no evidence from the included trials of a significant difference in analgesia or adverse effects between oxycodone and morphine or hydromorphone" (page 454). Caraceni 2011 reached a similar conclusion in their systematic review without meta-analysis. Bekkering 2011 and Reid 2006 both included meta-analyses in their systematic reviews and they also concluded that the effectiveness of oxycodone and morphine did not significantly differ. although the inclusion criteria employed by Bekkering 2011 differed from ours, with Bekkering 2011 excluding cross-over trials and including trials of chronic non-malignant pain, whereas the publication of Reid 2006 before the trial of Mercadante 2010 precluded its inclusion. That said, the conclusions of all these reviews are all in agreement with those that we have reached in this review dealing with the same comparisons as the aforementioned reviews.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with cancer pain: we found low quality evidence that oxycodone offers similar levels of pain relief and side effects as morphine for patients with cancer.

2. For clinicians: we found low quality evidence that oxycodone offers similar levels of cancer pain relief and adverse events to other strong opioids including morphine, which is commonly considered the gold standard strong opioid.

3. For policy makers: the findings of this review are consistent with current international guidance on using oxycodone or morphine as first line opioids for patients with cancer-related pain.

4. For funders: we did not undertake cost-effectiveness analysis.

Implications for research

1. General: we found that the current evidence base is comprised of studies that contain small numbers of patients in which there is a significant (20%) dropout rate. For example, the direct comparison meta-analysis between oxycodone and morphine is based on fewer than 300 cancer patients in each treatment group; this is a very small evidence base. However, given the absence of important differences within this analysis, it seems unlikely that larger head to head studies of oxycodone versus morphine will be justified.

2. Design: there were no implications for the design of future clinical studies.

3. Measurement (endpoints): for future cancer pain studies, developing a single outcome that combines good pain control (no more than mild on a verbal rating scale) with acceptable side effects (perhaps no more than mild severity on any adverse event) would enable a clearer comparison between any analgesics used in this context.

ACKNOWLEDGEMENTS

This article presents an extension to a systematic review undertaken as part of the 2011 National Institute for Health and Clinical Excellence (NICE) guideline on "Opioids in palliative care" (NICE 2012) which was developed by the National Collaborating Centre for Cancer (NCC-C). The NCC-C receives funding from NICE.

We would like to thank Yuhong Yuan (Department of Medicine, Division of Gastroenterology McMaster University, Canada) for help with the translation of Chinese papers and Joanne Abbott at PaPas for her assistance in devising and executing the search strategy.

Cochrane Review Group funding acknowledgement: the National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. Disclaimer: the views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health.

REFERENCES

References to studies included in this review

Beaver 1978 *{published data only}*

Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. I. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. *Journal of Pharmacology and Experimental Therapeutics* 1978;**207** (1):92–100.

Beaver 1978a *{published data only}*

Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular oxycodone with intramuscular morphine and codeine. *Journal of Pharmacology and Experimental Therapeutics* 1978;**207**(1): 101–8.

Bruera 1998 *{published data only}*

Bruera E, Belzile M, Pituskin E, Fainsinger R, Darke A, Harsanyi Z, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *Journal of Clinical Oncology* 1998;**16**(10): 3222–9.

Comerford T, Bruera E. Efficacy of controlled-release oxycodone. *Journal of Clinical Oncology* 1999;**17**:738.

Gabrail 2004 *{published data only}*

Gabrail NY, Dvergsten C, Ahdieh H. Establishing the dosage equivalency of oxymorphone extended release and oxycodone controlled release in patients with cancer pain: a randomized controlled study. *Current Medical Research and Opinion* 2004;**20**(6):911–8.

Gabrail NY, Dvergsten C, Ma T, Frailey A, Ahdieh H. Oxymorphone extended-release (ER) provides safe, effective, and rapid analgesia during opioid radiation: results of a randomized, double-blind, crossover, comparative study with oxycodone controlled-release (CR) [abstract]. *Proceedings of the American Society of Clinical Oncology* 2003: 737.

Hagen 1997 *{published data only}*

Hagen NA, Babul N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. *Cancer* 1997;**79**(7):1428–37.

Heiskanen 1997 *{published data only}*

Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. *Pain* 1997;**73**(1):37–45.

Heiskanen TE, Ruismaki PM, Seppala TA, Kalso EA. Morphine or oxycodone in cancer pain?. *Acta Oncologica* 2000;**39**(8):941–7.

Imanaka 2013 *{published data only}*

Imanaka K, Tominaga Y, Etropolski M, Van Hove I, Ohsaka M, Wanibe M, et al. Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain. *Current Medical Research and Opinion* 2013;**29**:1399–409.

Kalso 1990 *{published data only}*

Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clinical Pharmacology and Therapeutics* 1990;**47**(5):639–46.

Kalso E, Vainio A, Mattila MJ, Rosenberg PH, Seppala T. Morphine and oxycodone in the management of cancer pain: plasma levels determined by chemical and radioreceptor assays. *Pharmacology & Toxicology* 1990;**67** (4):322–8.

Kaplan 1998 *{published data only}*

Kaplan R, Parris WC, Citron ML, Zhukovsky D, Reder RF, Buckley BJ, et al. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *Journal of Clinical Oncology* 1998;**16**(10):3230–7.

Lauretti 2003 *{published data only}*

Lauretti GR, Oliveira GM, Pereira NL. Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients. *British Journal of Cancer* 2003;**89**(11):2027–30.

Leow 1995 *{published data only}*

Leow KP, Cramond T, Smith MT. Pharmacokinetics and pharmacodynamics of oxycodone when given intravenously and rectally to adult patients with cancer pain. *Anesthesia and Analgesia* 1995;**80**(2):296–302.

Mercadante 2010 *{published data only}*

Mercadante S, Tirelli W, David F, Arcara C, Fulfaro F, Casuccio A, et al. Morphine versus oxycodone in pancreatic cancer pain: a randomized controlled study. *Clinical Journal of Pain* 2010;**26**(9):794–7.

Mucci-LoRusso 1998 *{published data only}*

Mucci-LoRusso P, Berman BS, Silberstein PT, Citron ML, Bressler L, Weinstein SM, et al. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: A randomized, double-blind, parallel-group study. *European Journal of Pain* 1998;**2**(3): 239–49.

Parris 1998 *{published data only}*

Parris WC, Johnson BW Jr, Croghan MK, Moore MR, Khojasteh A, Reder RF, et al. The use of controlled-release oxycodone for the treatment of chronic cancer pain: a randomized, double-blind study. *Journal of Pain & Symptom Management* 1998;**16**(4):205–11.

Riley 2014 *{published data only}*

Riley J, Branford R, Droney J, Gretton S, Sato H, Kennett A, et al. Morphine or oxycodone for cancer-related pain? A randomised, open-label, controlled trial. *Journal of Pain and Symptom Management* 2014;**in press**.

Riley J, Branford R, Droney J, Gretton S, Sato H, Thick M, et al. A randomised controlled trial of oral morphine versus oral oxycodone for the treatment of pain in cancer patients. *Palliative Medicine* 2012;**26 (4)**:386.

Salzman 1999 *{published data only}*

Salzman RT, Roberts MS, Wild J, Fabian C, Reder RF, Goldenheim PD. Can a controlled-release oral dose form of

oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control?. *Journal of Pain and Symptom Management* 1999;**18**(4):271–9.

Stambaugh 2001 ***{published data only}***
Stambaugh JE, Reder RF, Stambaugh M. Double-blind, randomized, two-period crossover efficacy and pharmacokinetic comparison of immediate-release oxycodone (IR) and controlled-release oxycodone (CR) in cancer patients with pain. *Clinical Pharmacology and Therapeutics* 1997;**61**(2):197.
Stambaugh JE, Reder RF, Stambaugh MD, Stambaugh H, Davis M. Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate-release oral oxycodone in cancer pain patients. *Journal of Clinical Pharmacology* 2001;**41**(5):500–6.

References to studies excluded from this review

Ahmedzai 2012 ***{published data only}***
Ahmedzai Sam H, Nauck Friedemann, Bar-Sela Gil, Bosse Bjorn, Leyendecker Petra, Hopp Michael. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliative Medicine* 2012;**26**(1):50–60.

Chen 2009 ***{published data only}***
Chen HP, Jiang JJ, Li JX. [Efficacy and safety of oxycodone-acetaminophen for moderate and severe visceral pain in advanced cancer patients] LA: Chi. *Chinese Journal of New Drugs* 2009;**18**(10):920–2.

Dunlop 2013 ***{published data only}***
Dunlop W, Neufeld K. Quality of life benefits and cost impact of prolonged release oxycodone/naloxone versus prolonged release oxycodone in patients with moderate to severe pain and opioid-induced constipation despite the use of 2 laxatives: A UK cost utility analysis. *Value in Health* 2013;**16 (7)**:A384.

Garassino 2010 ***{published data only}***
Garassino MC, Febbraro A, Iorno V, Carbone A, Spagnoletti I, Isa L, et al. Randomized phase ii trial (NCT00637975) evaluating activity and toxicity of fixed dose of oxycodone and increasing dose of pregabalin versus increasing dose of oxycodone and fixed dose of pregabalin for the treatment of oncological neuropathic pain (neuropain-01). *Annals of Oncology* 2010;**21**:viii363.

Garassino 2011 ***{published data only}***
Garassino MC, Bianchi A, Febbraro A, Spagnoletti I, Iorno V, Bramati A, et al. Final results of a randomized phase II trial (NCT00637975) evaluating activity and toxicity of fixed-dose oxycodone and increasing dose of pregabalin versus increasing dose of oxycodone and fixed-dose pregabalin for the treatment of oncologic neuropathic pain (NEUROPAIN-01). *Journal of Clinical Oncology. Conference: ASCO Annual Meeting* 2011;**29**(15 Suppl 1).

Garassino 2013 ***{published data only}***
Garassino MC, Piva S, Verde N, Spagnoletti I, Iorno V, Carbone C, et al. Randomised phase II trial (NCT00637975) evaluating activity and toxicity of two different escalating strategies for pregabalin and oxycodone combination therapy for neuropathic pain in cancer patients. *PloS One* 2013, (4):e59981.

Leppert 2011 ***{published data only}***
Leppert W, Ahmedzai SH, Uhl R, Kremers W, Hopp M. Long-term efficacy and safety of the fixed combination oxycodone and naloxone prolonged release (PR) in patients with chronic cancer pain. *European Journal of Pain Supplements* 2011;**5 (1)**:172.

Li 2008 ***{published data only}***
Li RC, He BS. Therapeutic outcome of Tylox for cancer pain in malignant tumor patients with bone metastasis. [Chinese]. *Chinese Journal of New Drugs* 2008;**17**(18): 1619–21.

Li 2010 ***{published data only}***
Li XM, Liu DQ, Wu HY, Yang C, Yang L. Controlled-release oxycodone alone or combined with gabapentin for management of malignant neuropathic pain. *Chinese Journal of Cancer Research* 2010;**22**(1):80–6.

Meng 2008 ***{published data only}***
Meng Xl Tyzj. Effectiveness observation on oxycodone hydrochloride controlled-release tablets for cancer pain. *Modern Journal of Integrated Traditional Chinese and Western Medicine [Xian Dai Zhong Xi Yi Jie He Za Zhi]* 2008, (2): 199–200.

NCT01859715 ***{published data only}***
Emergency Department (ED) Drug Interaction in Emergency Department Patients. *Ongoing Trial* 2013.

NCT01885182 ***{published data only}***
Targin Cancer Pain. *Ongoing Trial* 2013.

Pang 2009 ***{published data only}***
Pang J, Jie BJ, Li YP. Efficacy of oxycodone-acetominophen by different administrations in controlling moderate to severe cancer pain and break-out pain. [Chinese]. *Chinese Journal of New Drugs* 2009;**18**(18):1767–70,1776.

Shi 2008 ***{published data only}***
Shi L, Xiong HH, Yang L, Yu SY. Analgesic effect of oxycodone-acetaminophen tablets in patients with cervical cancer. *Chinese Journal of New Drugs* 2008;**17**:1884–5.

Sima 2010 ***{published data only}***
Sima L, Wu X, Fang W. Oxycodone/acetaminophen combination tablet in patientswith metastatic bone pain: A randomized, double-blinded, placebo-controlled trial. *Annals of Oncology* 2010;**21**:378.

Sima 2010a ***{published data only}***
Sima L, Wu X, Fang W, Li F. Oxycodone/acetaminophen addition to constant opioids in metastatic bone pain: A randomized, double-blinded, controlled, multicenter trial. *Journal of Clinical Oncology. Conference* 2010;**28**(15 Suppl 1).

Sima 2012 *{published data only}*
Sima L, Fang WX, Wu XM, Li F. Efficacy of oxycodone/paracetamol for patients with bone-cancer pain: a multicenter, randomized, double-blinded, placebo-controlled trial. *Journal of Clinical Pharmacy and Therapeutics* 2012;**37**(1):27–31.

Stambaugh 1980 *{published data only}*
Stambaugh JEJ. Analgesic equivalence of Tylox® and Percodan®: Double-blind crossover study of patients with pain from malignancy. *Current Therapeutic Research, Clinical and Experimental* 1980, (2):302–8.

Stambaugh 1980a *{published data only}*
Stambaugh JEJ, Tejada F, Trudnowski RJ. Double-blind comparisons of zomepirac and oxycodone with aspirin phenacetin caffeine in cancer pain. *Journal of Clinical Pharmacology* 1980;**20**(4):261–70.

Stambaugh 1981 *{published data only}*
Stambaugh JE Jr, Sarajian C. Analgesic efficacy of zomepirac sodium in patients with pain due to cancer. *Journal of Clinical Pharmacology* 1981;**21**:501–7.

Stambaugh 1987 *{published data only}*
Stambaugh JE, McAdams J. Comparison of the efficacy and safety of oral xorphanol, acetaminophen/oxycodone and placebo in chronic cancer pain. *International Journal of Clinical Pharmacology and Therapeutics* 1987;**41**:229.

Stambaugh 1990 *{published data only}*
Stambaugh J, Drew J, Johnson J. Comparison of flurbiprofen (Ansaid), oxycodone APAP and placebo in cancer pain, after single and repeat oral doses. *Clinical Pharmacology and Therapeutics* 1990;**47**:187.

Wu 2009 *{published data only}*
Wu H, Ouyang QC, Liu LP, Wang PH. Safety and efficacy of oxycodone/acetaminophen in treatment of moderate and advanced cancer pain. [Chinese]. *Chinese Journal of Cancer Prevention and Treatment* 2009;**16**(18):1432–4.

Xiong 2008 *{published data only}*
Xiong J, Liang C, Wu X, Zhao YX, Fu L, Zhou YF. Efficacy and safety of oxycodone-acetaminophen tablet in 142 patients with different types of moderate and advanced cancer pain. [Chinese]. *Chinese Journal of New Drugs* 2008; **17**(21):1877–9,1900.

Zou 2009 *{published data only}*
Zou J, Wang Q, Liu L. [Efficacy of oxycodone-acetaminophen as an adjuvant of opioid analgesics for cancer pain] LA: Chi. *Chinese Journal of New Drugs* 2009, (10):923–4.

References to studies awaiting assessment

2012-001578-26 *{published data only}*

Aurilio 2009 *{published data only}*
Aurilio C, Sansone P, Pace MC, Passavanti MB, Romano SV, Pota V. Evaluation of efficacy and safety of prolonged-release oxycodone at different dosages for the treatment of severe chronic pain. *Pain Practice* 2009;**9**:103.

JapicCTI-090789/090/091 *{published data only}*

NCT00378937 *{published data only}*

NCT00726830 *{published data only}*

Song 2009 *{published data only}*
Song JF, Zhao YL, Zhou HM, Wang HJ, Li KY. Efficacies of oxycodone and morphine sulfate sustained-release tablets in treating moderate and severe cancer pain. [Chinese]. *Chinese Journal of New Drugs* 2009;**18**(4):337–9.

References to ongoing studies

2006-003151-21 *{published data only}*
Study to compare the tolerability of slow release oxycodone versus slow release morphine in the treatment of severe cancer pain. The study is geared towards a clinical practice improvement. Ongoing study Not reported.

2008-002273-12 *{published data only}*
Long term opioid administration in oncologic chronic pain: open label, prospective study on efficacy, safety and pharmacogenetic factors. Ongoing study Not reported.

2009-013118-28 *{published data only}*
Bukkaalinen fentanyyli syöpäpotilaiden toimenpidekivun hoidossa ("The buccal fentanyl in cancer pain management measure"). Ongoing study Not reported.

2010-020402-15 *{published data only}*
Randomised, double-blind, cross-over Phase III study to investigate the efficacy and safety of oxycodone after once daily administration of oxycodone HCl XL tablets in comparison to twice daily administration of Oxygesic® tablets in patients with chronic pain. Ongoing study 3 September 2010.

Elsayem 2010 *{published data only}*
Elsayem AF, Bain KT, Palmer JL, Bearden J, Fisch M. A randomized comparison of oral methadone as a "first-switch" opioid versus opioid switching between sustained-release morphine and oxycodone for oncology outpatients with pain management problems. *Journal of Clinical Oncology. Conference* 2010;**28**(15 Suppl 1).

JapicCTI-132338 *{published data only}*
DS-7113b phase III study A randomized double-blind comparison study with immediate release (IR) oxycodone in opioid-naive patients with cancer pain. 2013.

NCT00916890 *{published data only}*
Chronic Administration of Opioids in Cancer Chronic Pain:an Open Prospective Study on Efficacy, Safety and Pharmacogenetic Factors Influence. Ongoing study February 2009.

NCT01165281 *{published data only}*
A Randomized, Double-Blind, Active Controlled, Optimal Dose Titration, Multicenter Study to Evaluate the Safety and Efficacy of Oral JNS024 Extended Release (ER) in Japanese and Korean Subjects With Moderate to Severe Chronic Malignant Tumor Related Cancer Pain. Ongoing study August 2012.

NCT01205126 ***{published data only}***
A Randomized, Double-Blind, Active Controlled, Multi-center Study to Investigate the Safety and Efficacy of OROS Hydromorphone HCl Once-daily Compared With Oxycodone HCL Controlled-release Twice Daily in Subjects With Cancer Pain. Ongoing study December 2009.

NCT01675622 ***{published data only}***
A Comparative Study of Immediate-Release Oxycodone Capsules Versus Immediate-Release Morphine Tablets for the Treatment of Chinese Patients With Cancer Pain.. Ongoing study December 2010.

NCT01809106 ***{published data only}***
RCT Comparing the Analgesic Efficacy of 4 Therapeutic Strategies Based on 4 Different Major Opioids (Fentanyl, Oxycodone, Buprenorphine vs Morphine) in Cancer Patients With Moderate/Severe Pain, at the Moment of Starting 3rd Step of WHO Analgesic Ladder. Ongoing study April 2011.

NCT02084355 ***{published data only}***
Study of Opioid Rotation Versus Opioid Escalation in Patients With Moderate to Severe Cancer Pain. *Ongoing Trial* 2014.

UMIN000011756 ***{published data only}***
Randomized study of fentanyl citrate versus Oxycodone Hydrochloride Hydrate in patients with unresectable advanced pancreatic cancer. 2013.

Additional references

Bekkering 2011
Bekkering GE, Soares-Weiser K, Reid K, Kessels AG, Dahan A, Treede RD, Kleijnen J. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. *Current Medical Research and Opinion* 2011;**27**:1477–91.

Bennett 2008
Bennett MI. What evidence do we have that the WHO analgesic ladder is effective in cancer pain?. *Systematic Reviews in Pain Research; Methodology Refined*. McQuay HJ, Moore R, Kalso E (editors). Seattle: IASP Press, 2008: 303–13.

Breivik 2009
Breivik H, Cherny N, Collett B, de Conno F, Filbet M, Foubert AJ, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Annals of Oncology* 2009;**20**:1420–33.

Caraceni 2011
Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. *Palliative Medicine* 2011;**25**:402–9.

Caraceni 2012
Caraceni A, Hanks GW, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al. Use of opioid analgesics in the treatment of cancer pain: evidence based recommendations from the EAPC. *Lancet Oncology* 2012;**13**:e58–e68.

Deandrea 2008
Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Annals of Oncology* 2008;**19**:1985–91.

Gudin 2012
Gudin J. Opioid therapies and Cytochrome P450 interactions. *Journal of Pain and Symptom Management* 2012;**44**:S4–S14.

Higgins 2011
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration. Available from www.cochrane-handbook.org, 2011.

King 2011
King SJ, Reid C, Forbes K, Hanks G. S systematic review of oxycodone in the management of cancer pain. *Palliative Medicine* 2011;**25**:454–70.

Lagendam 2013
Langendam MW, Akl EA, Dahm P, Glasziou P, Guyatt G, Schünemann HJ. Assessing and presenting summaries of evidence in Cochrane Reviews. *Systematic Reviews* 2013;**2**: 81–9.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0*. Available from www.cochrane-handbook.org: The Cochrane Collaboration, 2011.

Leppert 2010
Leppert W. Role of oxycodone and oxycodone/naloxone in cancer pain management. *Pharmacological Report* 2010;**62**: 578–91.

NICE 2012
NICE. Opioids in palliative care CG140. *http://www.nice.org.uk/CG140* 2012:online.

Reid 2006
Reid CM, Martin RM, Sterne JAC, Davies AN, Hanks GW. Oxycodone for cancer-related pain: Meta-analysis of randomized controlled trials. *Archives of Internal Medicine* 2006;**166**:837–43.

RevMan 2014
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ventafridda 1987
Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer* 1987;**59**:851–6.

WHO 1986
World Health Organization (WHO). Cancer Pain Relief. WHO, Geneva 1986.

References to other published versions of this review

Reid 2010

Reid CM, Davies AN, Hanks GW, Martin RM, Sterne JAC. Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews* 2010, Issue 3. [DOI: 10.1002/14651858.CD003870.pub3]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Beaver 1978

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: USA
Participants	Patients: 17 patients entered, "13 patients completed at least one round" (see Interventions" below) and were analysed for efficacy ("The 4 patients who failed to complete a single round did so for reasons extraneous to the drugs under study"); 5 males/8 females, mean (range) age = 51 (23 to 68) years. "One of these patients appeared twice in the study, and 5 completed a second round, yielding 19 cross-over comparisons." Inclusion criteria: "The subjects were patients with a variety of malignant tumours on the wards of James Ewing Hospital. Each patient was first examined to ascertain the nature and location of his or her pain, the extent of disease, prior experience with narcotics and analgesic drugs and ability to communicate meaningful information about pain. At this time, the patient was also told how the studies were to be conducted and that, while all test medications might appear the same, they would actually include a number of different drugs, some probably more effective than others in relieving pain. Many of the patients had had some prior experience with oral or parenteral narcotics, and several had a history of sufficient recent narcotic use to warrant the assumption that they possessed some tolerance to narcotics. Patients were placed on a routine analgesic other than those included in the study during nonstudy hours, and, insofar as was possible, concomitant administration of psychoactive drugs was avoided." Exclusion criteria: See 'Inclusion criteria'. No other information provided.
Interventions	Oxycodone arm - Drug: Oxycodone + oral placebo - Dose/dosing: 5 mg - Formulation: Intramuscular - Route of administration: Intramuscular - Length of treatment: Appears to be single dose - Titration schedule: No titration. - Rescue medication: Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See 'Rescue medication' and 'Inclusion criteria' Comparison arm 1 - Drug: Oxycodone + oral placebo - Dose or dosing: 15 mg - Formulation: Intramuscular - Route of administration: Intramuscular - Length of treatment: Appears to be single dose - Titration schedule: No titration - Rescue medication: Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine

	analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See 'Rescue medication' and 'Inclusion criteria' Comparison arm 2 - Drug: Oxycodone + intramuscular placebo - Dose or dosing: 10 mg - Formulation: Immediate-release? - Route of administration: Oral - Length of treatment: Appears to be single dose - Titration schedule: No titration - Rescue medication: Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See 'Rescue medication' and 'Inclusion criteria' Comparison arm 3 - Drug: Oxycodone + intramuscular placebo - Dose or dosing: 30 mg - Formulation: Immediate-release? - Route of administration: Oral - Length of treatment: Appears to be single dose - Titration schedule: No titration - Rescue medication: Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See 'Rescue medication' and 'Inclusion criteria' - For cross-over trials, cross-over schedule: "Treatments were assigned to patients according to a series of randomly chosen Latin squares, and each study medication was administered on a separate day. Each patient received a low and a high dose of both the "standard" and the "test drug," chosen at equilog intervals. Unless a patient completed all doses of the crossover comparison or "round," his data were excluded from the relative potency analysis. After completing the first round, some patients were able to repeat the course, allowing for comparison of replicate rounds within the same individual."
Outcomes	- Pain intensity: Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication) "; using a 4-point categorical scale from 0 (= none) (1 = slight, 2 = moderate) to 3 (= severe) - Pain relief: Assessed by patient hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication); using a 5-point categorical scale from 0 (= none) (1 = slight, 2 = moderate, 3 = lots) to 4 (= complete) "Patients who were remedicated before 6 hr elapsed after administration of a study medication were assigned scores of zero (0) for change in pain intensity and pain relief for the remaining observation points of the 6-hr observation period." - Side effects: "The observer also recorded apparent and volunteered side-effects, but

Beaver 1978 (*Continued*)

	leading questions were avoided."
Notes	- Study free of commercial funding? No: "This work was supported by grants awarded by the Committee on Problems of Drug Dependence, National Academy of Sciences, National Research Council, from funds contributed by a group of interested pharmaceutical manufacturers, and by National Cancer Institute Grant CA-08748." - Groups comparable at baseline? No patient details reported by initial treatment allocation - ITT analyses undertaken? No: "Unless a patient completed all doses of the crossover comparison or "round," his data were excluded from the relative potency analysis"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Treatments were assigned to patients according to a series of randomly chosen Latin squares". No further information reported
Allocation concealment (selection bias)	Unclear risk	See cell above
Blinding of participants and personnel (performance bias) Pain	Low risk	"Neither the patient nor the observer was aware of the identity of the medications, which were physically indistinguishable and identified only by a numerical code on individual dosage envelopes. To maintain double-blind conditions, both capsules and an injection, one of which was a dummy, were administered each time a patient was given a study medication."
Blinding of participants and personnel (performance bias) Adverse events	Low risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Low risk	Patient reported. See cell above
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Patient reported. See cell above
Incomplete outcome data (attrition bias) Pain	Unclear risk	Data from 13/17 patients reported. "One of these patients appeared twice in the study, and 5 completed a second round, yielding 19 crossover comparisons."

Beaver 1978 (*Continued*)

Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Data from 13/17 patients reported. "One of these patients appeared twice in the study, and 5 completed a second round, yielding 19 crossover comparisons."
Selective reporting (reporting bias)	High risk	No side effects or adverse events reported in detail: "The side-effects are both intramuscular and oral oxycodone were dose-related and qualitatively similar to those noted in the codeine study." (which were also not reported in any detail at all: "While a dose-response regression was generally evident, side-effects did not occur with sufficient frequency to allow meaningful analysis.")
Other bias	Unclear risk	It is unclear if this study is subject to a high risk of other biases
Were the patients adequately titrated?	Unclear risk	Not enough information provided
For cross-over trials: Are data available for both time periods?	Low risk	Yes,data are available from all the cross-over periods

Beaver 1978a

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: USA
Participants	"The patient population and method of evaluating analgesic efficacy were similar to those employed in the oral/parenteral analgesic relative potency assays of codeine and oxycodone described in the previous paper" Beaver 1978 This paper contains 2 studies: 'Intramuscular morphine and oxycodone' and 'intramuscular codeine, oxycodone and morphine' 'Intramuscular morphine and oxycodone' Patients: 34 patients entered, "28 patients completed at least one round" (see Interventions" below) and were analysed for efficacy ("All of the patients who failed to complete a single round did so for reasons extraneous to the drugs under study"); 14 males/14 females, mean (range) age = 46 (23 to 68) years. "Of the 28 patients participating in the study, 4 appeared twice in a single series, and 2 appeared in each of two series. Twenty-four patients completed a second round, yielding a total of 58 crossover comparisons." 'Intramuscular codeine, oxycodone and morphine' Patients: 30 patients entered, "26 completed at least one round" (see Interventions" below) and were analysed for efficacy ("The 4 who failed to complete a single round did so for reasons extraneous to the drugs under study"); 14 males/12 females, mean (range) age = 45 (23 to 80) years. "Series I was carried out in 11 patients, one of whom appeared twice in the series and 10 of whom completed a second round, yielding 22 cross-over

	comparisons of 90 and 180 mg of codeine, 7.5 and 15 mg of oxycodone and 16 mg of morphine. Series II consisted of 27 cross-over comparisons in 16 patients of 90 and 180 mg codeine, 15 and 30 mg of oxycodone, and 16 mg of morphine. One patient appeared in both Series I and Series II." Inclusion criteria: See above Exclusion criteria: See above
Interventions	**'Intramuscular morphine and oxycodone':** "This assay consisted of three series, each comparing two doses of morphine sulfate (the standard) with two doses of oxycodone hydrochloride (the test drug) by intramuscular injection." "The distribution of patients and doses in the various series is presented in table 1. In general, the more obviously tolerant patients were given series II treatments, which consisted of double the dosage in series I." Oxycodone arm - Drug: Oxycodone hydrochloride - Dose or dosing: Series I: 7.5 mg and 15 mg; Series II and III: 15 mg and 30 mg - Formulation: Intramuscular - Route of administration: Intramuscular - Length of treatment: Appears to be single dose - Titration schedule: No titration - Rescue medication: "Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See "Rescue medication" and "Inclusion criteria" Comparison arm - Drug: Morphine sulfate - Dose or dosing: Series I and III: 8 mg and 16 mg; Series II: 16 mg and 32 mg - Formulation: Intramuscular - Route of administration: Intramuscular - Length of treatment: Appears to be single dose - Titration schedule: No titration - Rescue medication: "Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See "Rescue medication" and "Inclusion criteria" **'Intramuscular codeine, oxycodone and morphine':** "This assay consisted of two series, each comparing 90 and 180 mg codeine phosphate (the standard) with two doses of oxycodone hydrochloride (the test drug) and a single 16 mg dose of morphine sulfate." Oxycodone arm - Drug: Oxycodone hydrochloride - Dose or dosing: Series I: 7.5 mg and 15 mg; Series II: 15 mg and 30 mg - Formulation: Intramuscular - Route of administration: Intramuscular - Length of treatment: Appears to be single dose - Titration schedule: No titration - Rescue medication: "Assessed by patient "hourly for 6 hours after administration of

	the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See "Rescue medication" and "Inclusion criteria" Comparison arm 1 - Drug: Morphine sulfate - Dose or dosing: Series I and II: 16 mg - Formulation: Intramuscular - Route of administration: Intramuscular - Length of treatment: Appears to be single dose - Titration schedule: No titration - Rescue medication: "Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See 'Rescue medication' and 'Inclusion criteria' Comparison arm 2 - Drug: Codeine phosphate - Dose/dosing: Series I and II: 90 mg and 180 mg - Formulation: Intramuscular - Route of administration: Intramuscular - Length of treatment: Appears to be single dose - Titration schedule: No titration - Rescue medication: "Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication)". No further information reported - Other medication: See 'Rescue medication' and 'Inclusion criteria' - For cross-over trials, cross-over schedule: "Treatments were assigned to patients according to a series of randomly chosen Latin squares, and each study medication was administered on a separate day. Each patient received a low and a high dose of both the "standard" and the "test drug," chosen at equilog intervals. Unless a patient completed all doses of the cross-over comparison or "round," his data were excluded from the relative potency analysis. After completing the first round, some patients were able to repeat the course, allowing for comparison of replicate rounds within the same individual."
Outcomes	- Pain intensity: Assessed by patient "hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication) "; using a 4-point categorical scale from 0 (= none) (1 = slight, 2 = moderate) to 3 (= severe) - Pain relief: Assessed by patient hourly for 6 hours after administration of the study medication or until pain returned to the premedication level and a routine analgesic was administered (if at least 3 hr had elapsed since administration of the study medication); using a 5-point categorical scale from 0 (= none) (1 = slight, 2 = moderate, 3 = lots) to 4 (= complete) "Patients who were remedicated before 6 hr elapsed after administration of a study medication were assigned scores of zero (0) for change in pain intensity and pain relief for the remaining observation points of the 6-hr observation period."

	- Side effects: "The observer also recorded apparent and volunteered side-effects, but leading questions were avoided."
Notes	- Study free of commercial funding? No: "This work was supported in part by grants awarded by the Committee on Problems of Drug Dependence, National Academy of Sciences, National Research Council, from funds contributed by a group of interested pharmaceutical manufacturers, and by National Cancer Institute Grant CA-08748." - Groups comparable at baseline? No patient details reported by initial treatment allocation - ITT analyses undertaken? No: "Unless a patient completed all doses of the crossover comparison or "round," his data were excluded from the relative potency analysis"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Treatments were assigned to patients according to a series of randomly chosen Latin squares". No further information reported
Allocation concealment (selection bias)	Unclear risk	See cell above
Blinding of participants and personnel (performance bias) Pain	Low risk	"Neither the patient nor the observer was aware of the identity of the medications, which were physically indistinguishable and identified only by a numerical code on individual dosage envelopes. To maintain double-blind conditions, both capsules and an injection, one of which was a dummy, were administered each time a patient was given a study medication." From Beaver 1978
Blinding of participants and personnel (performance bias) Adverse events	Low risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Low risk	Patient reported. See cell above
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Patient reported. See cell above
Incomplete outcome data (attrition bias) Pain	Unclear risk	Data included from 28/34 and 26/30 patients in the two studies, respectively

Beaver 1978a (*Continued*)

Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Data included from 28/34 and 26/30 patients in the two studies, respectively
Selective reporting (reporting bias)	High risk	No side effects or adverse events reported in detail: Study 1: "While side-effects observed after both morphine and oxycodone were typical of the narcotic analgesics, they did not occur with sufficient frequency to allow a meaningful comparison of the side-effect liability of the two drugs. Noteworthy was the virtual absence of side-effects in patients in series II, an observation consistent with these patients' substantial tolerance to narcotics." Study 2: "Side-effects were qualitatively similar to those noted in the oxycodone-morphine comparison, but they did not occur with sufficient frequency to allow a meaningful comparison among treatments."
Other bias	Unclear risk	It is unclear if this study is subject to a high risk of other biases
Were the patients adequately titrated?	Unclear risk	Not enough information provided
For cross-over trials: Are data available for both time periods?	Low risk	Yes, data are available from all the cross-over periods

Bruera 1998

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: Canada
Participants	Patients: 32 patients entered, 23 patients analysed for efficacy and VAS variables (5 patients dropped out during the CR morphine phase: 3 in phase 1, 2 in phase 2; 1 due to lack of pain control and adverse event, 1 due to protocol violation, 3 due to adverse events; 4 patients dropped out during the CR oxycodone phase: 2 in phase 1, 2 in phase 2; 1 due to lack of pain control, 2 due to adverse events, 1 was lost to follow-up) ; 13 females, 10 males; age not reported; cancer type: lung (7), breast (7), prostate (1) , other (8): cancer stage not reported; type of pain not reported; setting: palliative care programme; previous analgesic medication: IR morphine (8), CR morphine (10), IR oxycodone ± acetaminophen (11), CR hydromorphone (1), CR codeine (1), IR codeine + acetaminophen (1); duration of opioid use: 6.6 (± 10) months; duration of chronic pain: 8 (± 13) months Inclusion criteria: "The study included 32 patients from the Palliative Care Program at the Cross Cancer Institute and Grey Nuns Hospital in Edmonton, Canada. All patients were ≥ 18 years of age, gave written informed consent, had pain due to cancer, and were

	receiving treatment with an oral opioid analgesic at study entry. Life expectancy for all patients was estimated by the treating physician to be at least 4 months." Exclusion criteria: Use of active anticancer therapy, with the exception of hormones, within 2 weeks of study entry; physical or mental inability to answer questions and comply with the treatment protocol; history of intolerance of oxycodone or any related compound; impaired renal or hepatic function; significantly impaired ventilatory function (clinically present dyspnea at rest); current use of an investigational drug; pregnancy or lactation; unwillingness or inability to co-operate or give written, informed consent; and inability to take oral medications
Interventions	Oxycodone arm - Drug: Oxycodone + placebo morphine - Dose and dosing: Mean dose = 46.5 (± 57) mg every 12 hours - Formulation: Controlled-release (CR) - Route of administration: Oral - Length of treatment: 7 days - Titration schedule: "≥ 3 day prestudy history of stable analgesia (defined as a daily rescue opioid consumption ≤ 20% of the scheduled daily opioid dose)" - Rescue medication: Immediate-release oxycodone hydrocloride, at doses of ca 10% of daily scheduled opioid dose. Mean daily number of doses = 2.3 (± 2.3) - Other medication: No other analgesic agents. All other pre-study medications were maintained with no changes allowed later than 72 hours before randomisation Comparison arm - Drug: Morphine + placebo oxycodone - Dose and dosing: Mean dose = 72.6 (± 102) mg every 12 hours - Formulation: Controlled-release (CR) - Route of administration: Oral - Length of treatment: 7 days - Titration schedule: "≥ 3 day prestudy history of stable analgesia (defined as a daily rescue opioid consumption ≤ 20% of the scheduled daily opioid dose)" - Rescue medication: Immediate-release (IR) morphine, at doses of ca 10% of daily scheduled opioid dose. Mean daily number of doses = 1.7 (± 2.1) - Other medication: No other analgesic agents, all other pre-study medications were maintained with no changes allowed later than 72 hours before randomisation "Patients who had been receiving narcotic analgesics other than morphine or single-entity oxycodone before the start of the study were transferred to an equianalgesic oral dose of controlled-release oxycodone or controlled-release morphine at the start of phase 1. The initial dose of controlled-release oxycodone was determined busing a 1:1.5 conversion ratio between controlled-release oxycodone and controlled-release morphine" - For cross-over trials, cross-over schedule: On day 8 patients were crossed over to receive the alternative drug and placebo at a dose equivalent to that received at the start of phase 1. During both study phases, blind-labelled dose adjustments were permitted if patients required more than 3 rescue analgesic doses over 24 hours
Outcomes	- Pain intensity: Assessed by patient 4 times per day before dosing and at the end of each phase; 100 mm VAS (0 = no pain to 100 = worst possible pain) and 5-point categorical scale (0 = no pain to 4 = worst possible pain) - Overall effectiveness of the study medication: Assessed by patient on days 8 and 15; verbal rating scale (0 = not effective to 3 = highly effective)

	- Nausea and sedation: Days 8 and 15; 100 mm VAS (0 = no nausea or sedation to 100 extreme nausea or sedation) - Adverse events: Recorded by patients; checklist (nausea, vomiting, constipation, dry mouth, drowsiness, dizziness, difficulty concentrating, fatigue, poor sleep, vivid dreams, hallucinations, headache, agitation, twitching, itching, sweating; rated from 0 (= none) to 4 (intolerable)) and non-directed adverse events questionnaire - Treatment preference: Assessed by patients and investigators at the end of study
Notes	- Study free of commercial funding? Unclear. No information provided - Groups comparable at baseline? No patient details reported by initial treatment allocation - ITT analyses undertaken? No for efficacy or VAS variables where the analyses restricted to the 23/32 patients who completed both study phases. Satefy variables were analysed for all enrolled patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomised. No further information provided
Allocation concealment (selection bias)	Unclear risk	See cell above
Blinding of participants and personnel (performance bias) Pain	Low risk	"Blinding was maintained by the double-dummy technique using matching placebos of controlled release oxycodone and controlled-release morphine. The immediate-release oxycodone and morphine formulations were also blinded." Trial labelled as 'double-blind'
Blinding of participants and personnel (performance bias) Adverse events	Low risk	"Blinding was maintained by the double-dummy technique using matching placebos of controlled release oxycodone and controlled-release morphine. The immediate-release oxycodone and morphine formulations were also blinded." Trial labelled as 'double-blind'
Blinding of outcome assessment (detection bias) Pain	Low risk	See cell above. Outcome was patient-reported
Blinding of outcome assessment (detection bias) Adverse events	Low risk	See cell above. Outcome was patient-reported

Bruera 1998 (*Continued*)

Incomplete outcome data (attrition bias) Pain	High risk	23/32 patients analysed
Incomplete outcome data (attrition bias) Adverse events	High risk	The only safety data analyses that are reported analysed 23/32 patients
Selective reporting (reporting bias)	High risk	The majority of the adverse events are not reported beyond the sentence "There were no statistically significant differences by treatment in mean severity for any of the elicited adverse events or in frequency of reporting of unelicited events."
Other bias	Low risk	The authors report that "There was no evidence of period or sequence (carry-over) effect." No other biases were identified
Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated
For cross-over trials: Are data available for both time periods?	Low risk	Yes. Data only analysed if available from both time periods

Gabrail 2004

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: USA
Participants	Patients: 58 patients screened, 47 patients titrated, 45 patients randomised, and 44 patients received ≥ 1 dose of study medication and had ≥ 1 pain intensity evaluation after treatment and were therefore analysed for safety (1/45 never received any double-blind study medication and was excluded from all analyses). A total of 37/45 randomised patients completed the first double-blind phase and ≥ 5 days of the second phase and were analysed for efficacy (2/45 patients had insufficient visits or assessments to be included in the efficacy population); 5/45 randomised patients discontinued the drug during the double-blind treatment periods: 2 patients withdrew due to adverse events unrelated to the study drug, 2 patients withdrew consent and 1 patient due to protocol violation. No patients discontinued the study due to insufficient analgesia or loss to follow-up A total of 21 safety and 18 efficacy patients received extended-release oxymorphone followed by controlled-release oxycodone and 23 safety and 19 efficacy patients received controlled-release oxycodone followed by extended-release oxymorphone A total of 21 men and 23 women, mean age (range) = 59.3 (26 to 81) years; 80% had severe untreated pain and 20% had moderate untreated pain. Previous anticancer therapy included surgery (68%), chemotherapy (82%), radiotherapy (50%), and/or immunotherapy (2.3%) Inclusion criteria: Men and women aged ≥ 18 years with moderate to severe pain secondary to cancer who required long-term outpatient treatment with an opioid analgesic.

	Patients hospitalised for reasons unrelated to cancer were also eligible Exclusion criteria: Allergy or sensitivity to morphine, extended-release oxymorphone, controlled-release oxycodone or their components, requirement for a concurrent opioid analgesic other than the study medication, contraindication to opioid therapy, pregnancy, lactation, plan for pregnancy, uncontrolled emesis, inability to take adequate oral food and hydration, levels of hepatic enzymes (gamma-glutamyl transpeptidase, alanine aminotransferase, and aspartate animotransferase) $\geq$ 3 times the upper limit of the normal range, receipt of radiotherapy or therapeutic radionuclides within the previous 2 weeks preceding study enrolment
Interventions	Oxycodone arm - Drug: Oxycodone - Dose and dosing: Mean daily dose = 91.9 mg (any dose adjustments were made during the first 3 days of the double-blind phase; dosage remained fixed thereafter) - Formulation: Controlled-release (CR) - Route of administration: Oral - Length of treatment: 7 to 10 days, take medication at 8 am and 8 pm - Titration schedule: "During the open-label titration/stabilization phase, patients received either oxymorphone immediate-release (IR) or oxycodone CR to determine a stable dosage, defined as a fixed dosage that provided adequate analgesia for at least 2 consecutive days, required no more than 2 doses of rescue medication/day, and produced tolerable AEs." - Rescue medication: Tablets of 15 mg oral morphine sulfate (IR) every 4 to 6 hours as needed. Patients requiring > 2 doses/day after the first 3 days of double-blind treatment were discontinued. Mean daily dose (range) = 12.6 (0 to 75) mg - Other medication: Not reported Comparison arm - Drug: Oxymorphone - Dose and dosing: Mean daily dose = 45.9 mg (any dose adjustments were made during the first 3 days of the double-blind phase; dosage remained fixed thereafter) - Formulation: Extended-release, take medication at 8 am and 8 pm - Route of administration: Oral - Length of treatment: 7 to 10 days - Titration schedule: "During the open-label titration/stabilization phase, patients received either oxymorphone immediate-release (IR) or oxycodone CR to determine a stable dosage, defined as a fixed dosage that provided adequate analgesia for at least 2 consecutive days, required no more than 2 doses of rescue medication/day, and produced tolerable AEs." - Rescue medication: Tablets of 15 mg oral morphine sulfate (IR) every 4 to 6 hours as needed. Patients requiring > 2 doses/day after the first 3 days of double-blind treatment were discontinued. Mean daily dose (range) = 16.6 (0 to 90) mg - Other medication: Not reported - For cross-over trials, cross-over schedule: "Following the first double-blind treatment period, patients crossed over to the alternative double-blind treatment (oxymorphone ER or oxycodone CR) for an additional 7-10 days."
Outcomes	- Pain intensity: Assessed by daily diary recording by the patients of all study drugs taken (including supplemental pain medication) and their 24-hour pain intensity, using an 11-point numerical scale (0 = no pain to 10 = worst possible pain) and the Brief Pain

Gabrail 2004 (*Continued*)

	Inventory - Quality of life: Assessed by the Brief Pain Inventory to assess the interference of pain with 7 domains of quality of life (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life). Appears to be rated by the patients during the study visits that marked the end of each double-blind treatment phase - Global assessment of current pain medication, rated by patients and physicians independently following each double-blind phase. Physicians were asked "Please rate the subject's current pain medication used for treating their cancer pain" - Karnofsky performance status: assessed by physicians at each visit - Safety analysis: Assessed by physical examination, vital signs, clinical laboratory tests (serum chemistry profile, complete blood count, urinanalysis), electrocardiograms and the monitoring of adverse events (which were rated by the investigators as mild, moderate, severe intensity, and as unlikely, possibly, probably related to study medication)
Notes	- Study free of commercial funding? No, the study was funded by Endo Pharmaceuticals Inc., Chadds Ford, PA and Penwest Pharmaceuticals Co., Danbury, CT - Groups comparable at baseline? The authors report that there were no significant differences in the demographic or baseline characteristics of the treatment groups, but do not report these characteristics split by treatment group - ITT analyses undertaken? No for efficacy and safety where the analyses were restricted to 37 and 41 to 43 of 45 randomised patients, respectively

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomised. No further information provided
Allocation concealment (selection bias)	Unclear risk	See cell above
Blinding of participants and personnel (performance bias) Pain	Unclear risk	The study is described as "double-blind". No further information reported, so it is unclear who was blinded and whether it was adequately executed
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Unclear risk	See cell above
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	See cell above

Gabrail 2004 (*Continued*)

Incomplete outcome data (attrition bias) Pain	High risk	37/45 randomised patients were analysed for efficacy
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	41 to 43 of 45 randomised patients were analysed for efficacy
Selective reporting (reporting bias)	Low risk	The main expected outcomes are reported
Other bias	Low risk	The authors report that "There were no sequence effects observed during the study; comparable pain scores and other efficacy measures were obtained irrespective of the order in which patients received the study medication." No other potential biases were identified
Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated
For cross-over trials: Are data available for both time periods?	Low risk	Yes, data are available for both study periods for 40/45 patients

Hagen 1997

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: Canada
Participants	Patients: 44 patients enrolled, 31 patients completed the study. Reasons for withdrawal included adverse events (N = 8), inadequate pain control (N = 3), intercurrent illness (N = 1) and voluntary withdrawal (N = 1). "Failure to complete both phases of the study did not appear to be related to toxicity of one of the study drugs over another." The analysis of all efficacy outcome variables, including VAS and categorical pain intensity, sedation, VAS and nausea VAS were restricted to patients completing both study phases. Spontaneously reported safety variables were analysed for all enrolled patients 13 men/18 women, mean age (SE) = 56 (3) years. Primary tumour: Breast (N = 7), colorectal (N = 5), lung (N = 1), urological/prostate (N = 5), CNS (N = 4), unknown primary (N = 2), other (N = 7). Type of pain: Bone (61%, soft tissue (29%), visceral (23%), neuropathic (45%). Pain described as "lancinating" (16%): steady pain (61%), incident pain with or without steady pain (52%) Inclusion criteria: Patients with chronic cancer pain and stable analgesic requirements Exclusion criteria: Known hypersensitivity to opioid analgesics, intolerance of oxycodone or hydromorphone, presence of a medical or surgical condition likely to interfere with drug absorption in the gastrointestinal tract, concurrent use of other opioid analgesics during the study period, presence of intractable nausea and vomiting, and patients who had undergone or were expected to undergo therapeutic procedures likely to influence their pain during the study period

Hagen 1997 (*Continued*)

Interventions	Oxycodone arm - Drug: Oxycodone - Dose and dosing: Mean daily initial dose = 120 ± 22 mg, mean final dose = 124 ± 22 mg (blind-label dose changes were permitted, and in case of a dose change, the rescue analgesic dose was modified accordingly) - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 7 days, 12-hourly - Titration schedule: "Patients with 3 days of stable analgesic requirements on a prestudy opioid were randomized to controlled-release oxycodone or controlled-release hydromorphone. Stable analgesia was defined as 2 or fewer rescue doses of opioid analgesic per 24-hour period, calculated over 3 or more days." - Rescue medication: Incident and nonincident breakthrough pain was treated with immediate-release oxycodone at a dosage of approximately 10% of the daily scheduled dose. Mean daily frequency of rescue use (SD) = 1.4 ± 0.3 mg - Other medication: No other opioids were permitted. Nonopioid analgesics, such as corticosteriods, antidepressants, anticonvulsants, bisphosphonates and psychostimulants, that had been part of the patient's therapy were continued at the same dose level throughout the study Comparison arm - Drug: Hydromorphone - Dose/dosing: Mean daily initial dose = 24 ± 4 mg, mean final dose = 30 ± 6 mg (blind-label dose changes were permitted, and in case of a dose change, the rescue analgesic dose was modified accordingly) - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 7 days, 12-hourly - Titration schedule: "Patients with 3 days of stable analgesic requirements on a prestudy opioid were randomized to controlled-release oxycodone or controlled-release hydromorphone. Stable analgesia was defined as 2 or fewer rescue doses of opioid analgesic per 24-hour period, calculated over 3 or more days." - Rescue medication: Incident and nonincident breakthrough pain was treated with immediate-release hydromorphone at a dosage of approximately 10% of the daily scheduled dose. Mean daily frequency of rescue use (SD) = 1.6 ± 0.3 mg - Other medication: No other opioids were permitted. Nonopioid analgesics, such as corticosteroids, antidepressants, anticonvulsants, bisphosphonates and psychostimulants, that had been part of the patient's therapy were continued at the same dose level throughout the study - For cross-over trials, cross-over schedule: "At the end of Phase I, patients were crossed over to the alternative treatment in Phase II without an intervening washout period."
Outcomes	- Pain intensity: Assessed by patients 4 times daily (8.00, 12.000, 16.00, and 20.00) on a 100 mm visual analogue scale (going from no pain to excruciating pain) and on a 5-point categorical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = excruciating) - Nausea and sedation: Assessed by patients 4 times daily (8.00, 12.000, 16.00, and 20.00) on a 100 mm visual analogue scale (going from no nausea or sedation to severe nausea or extreme sedation) - Spontaneuosly reported, investigator-observed and elicited adverse events were recorded at the end of each phase

Hagen 1997 (*Continued*)

	- Patient and investigator treatment preferences were recorded at the end of both phases
Notes	- Study free of commercial funding? No information reported, but the second author (Najib Babul) is an employee of Purdue Frederick, which is the manufacturer of the controlled-release oxycodone study drug used in the study - Groups comparable at baseline? No information provided about initial group allocation - ITT analyses undertaken? No for efficacy where the analyses were restricted to 31/44 patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) Pain	Low risk	"Blinding was maintained by the double-dummy technique, which involved matching placebos. In the active treatment phases, patients received either active controlled-release oxycodone and placebos matching controlled-release hydromorphone or active controlled-release hydromorphone and placebos matching controlled-release oxycodone."
Blinding of participants and personnel (performance bias) Adverse events	Low risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Low risk	See cell above
Blinding of outcome assessment (detection bias) Adverse events	Low risk	See cell above
Incomplete outcome data (attrition bias) Pain	High risk	The analyses were restricted to 31/44 patients
Incomplete outcome data (attrition bias) Adverse events	High risk	The analyses were restricted to 31/44 patients, or not reported in a manner that allowed them to be included in any meta-analysis

Hagen 1997 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	The adverse event reporting is restricted to 4 adverse events in a manner that allows them to be included in any meta-analysis
Other bias	Low risk	The authors reported that analysis of treatment sequence revealed no significant carry-over effects
Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated
For cross-over trials: Are data available for both time periods?	Low risk	Yes, data are available for both study periods for 31/44 patients

Heiskanen 1997

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: Finland
Participants	Patients: 45 patients enrolled, and 27/45 patients were evaluated for efficacy and safety. Reasons for withdrawal included adverse events (all were nausea/vomiting; N = 7), unstable pain control at the end of titration (N = 5), non-compliance (N = 3), sudden deterioration unrelated to the study (N = 1), and a technical error (N = 1); 1 patient was withdrawn due to suspected incomplete absorption of controlled-release oxycodone 16 men/11 women, mean age (range) = 60 (39-76) years. Primary tumour: Breast (N = 2), rectum (N = 5), lung (N = 4), prostate (N = 6), kidney (N = 1), pancreas (N = 4) , unknown primary (N = 2), other (N = 3). Former analgesics: Morphine alone or in combination with other analgesic (N = 20), oxycodone alone or in combination with other analgesic (N = 5). 12 patients were randomised to titration with CR oxycodone and 15 patients with CR morphine Inclusion criteria: Patients with chronic cancer pain requiring opioid analgesics, who were co-operative, and able to take oral medication and keep a simple diary Exclusion criteria: Patients receiving radiation therapy or other cancer treatment that could affect their pain
Interventions	Oxycodone arm - Drug: Oxycodone + morphine-matched placebo - Dose and dosing: Mean daily initial dose = 123 mg at the end of titration - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 3 to 6 days, unclear how many doses per day - Titration schedule: In opioid-naive patients the open-label titration phase (of 21-day maximum duration) was started with a total daily dose of 40 mg oxycodone. Dose titration was continued until effective pain relief with acceptable adverse effects was achieved for $\geq$ 48 hours. The controlled-release dose was titrated upwards if pain continued at the moderate to severe level or if > 2 dose of escape analgesic were used in a 24-hour period. The controlled-release dose was titrated downwards in case of unacceptable opioid

	adverse effects which were not manageable with appropriate treatment - Rescue medication: Oxycodone hydrocloride solution in a dose of approximately 1/6 to 1/8 of the daily dose of controlled-release oxycodone; mean total amount per patient during the last 3 days of the titration phase = 79 mg. Mean daily number of doses (SE) during double-blind phase = 1.26 ± 0.22 mg - Other medication: Non-steroidal anti-inflammatory analgesics, if used by the patient before the study, were continued at the same dose Comparison arm - Drug: Morphine + oxycodone-matched placebo - Dose and dosing: Mean daily initial dose = 180 mg at the end of titration - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 3 to 6 days, unclear how many doses per day - Titration schedule: In opioid-naive patients the open-label titration phase (of 21-day maximum duration) was started with a total daily dose of 40 mg oxycodone. Dose titration was continued until effective pain relief with acceptable adverse effects was achieved for ≥ 48 hours. The controlled-release dose was titrated upwards if pain continued at the moderate to severe level or if > 2 dose of escape analgesic were used in a 24-hour period. The controlled-release dose was titrated downwards in case of unacceptable opioid adverse effects which were not manageable with appropriate treatment - Rescue medication: Morphine hydrochloride solution in a dose of approximately 1/6 to 1/8 of the daily dose of controlled-release morphine; mean total amount per patient during the last 3 days of the titration phase = 74 mg. Mean daily number of doses (SE) during double-blind phase = 0.79 ± 0.18 mg - Other medication: Non-steroidal anti-inflammatory analgesics, if used by the patient before the study, were continued at the same dose - For cross-over trials, cross-over schedule: After 3 to 6 days of dosing, the patient visited the Pain Relief Unit for an end of phase visit. A similar 3 to 6 day period was then completed in a cross-over fashion using the other opioid
Outcomes	- Pain intensity: Assessed by patients 4 times daily (morning, noon, evening, and bedtime) on a 4-point verbal rating scale (none, slight, moderate, severe) - Acceptability of therapy: Assessed by patients twice daily, considering pain intensity and adverse effects during the previous 12-hour period on a 5-point verbal rating scale (very poor, poor, fair, good, excellent) - Adverse experiences: Recorded by patient in diary along with each dose of scheduled and escape study medication, concomitant medications, and intercurrent illnesses - At each double-blind phase ends, a Modified Specific Drug Effect Questionnaire was completed by the patients and a trained research nurse or investigator
Notes	- Study free of commercial funding? No, the study was funded by Purdue Frederick, which is the manufacturer of the controlled-release oxycodone study drug used in the study, and the Academy of Finland - Groups comparable at baseline? No information provided about initial group allocation - ITT analyses undertaken? No, the analyses were restricted to 27/45 patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Heiskanen 1997 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Computer generated randomisation for the open-label titration phase and again for the double-blind phase was performed by the Purdue Frederick Company and a list of randomisation codes was kept by the hospital pharmacist."
Allocation concealment (selection bias)	Low risk	See cell above. No further details reported. Probably adequate
Blinding of participants and personnel (performance bias) Pain	Low risk	A double-blind placebo controlled design was used. It is unclear who was blinded, but it appears that at least the patients were
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Low risk	Patient-reported. See also cell above
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	See cell above
Incomplete outcome data (attrition bias) Pain	High risk	The analyses were restricted to 27/45 patients
Incomplete outcome data (attrition bias) Adverse events	High risk	The analyses were restricted to 27/45 patients
Selective reporting (reporting bias)	Low risk	All expected main outcomes appear to be reported
Other bias	Low risk	It is unclear whether there were any carry-over effects, but there probably were none
Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated
For cross-over trials: Are data available for both time periods?	Low risk	Yes, data are available for both study periods for 27/45 patients

Imanaka 2013

Methods	Design: Randomised, double-blind, parallel-group multicentre non-inferiority trial Year: 25 August 2010 to 16 August 2012 Country: Japan, Korea
Participants	Patients: 343 patients enrolled, and 340/343 patients received ≥ 1 dose of study drug (N = 172 oxycodone, and N = 168 tapentadol); 236/343 patients completed treatment (N = 123 oxycodone, and N = 113 tapentadol), and 231/343 patients completed the study (N = 121 oxycodone, and N = 110 tapentadol). Reasons for withdrawal included adverse events (N = 14 oxycodone, and N = 12 tapentadol), progressive disease (N = 15 oxycodone, and N = 11 tapentadol), withdrawal of consent (N = 8 oxycodone, and N = 8 tapentadol), physician decision (N = 1 oxycodone, and N = 8 tapentadol), protocol violation (N = 5 oxycodone, and N = 5 tapentadol), lack of efficacy (N = 1 oxycodone, and N = 4 tapentadol), non-compliance (N = 4 oxycodone, and N = 1 tapentadol), death (N = 1 oxycodone, and N = 0 tapentadol), other (N = 0 oxycodone, and N = 6 tapentadol) Oxycodone: N = 172, 100 men and 72 women, mean age (SD) = 64.9 (11.41) years, 110 Japanese and 62 Korean. Primary tumour: gastrointestinal: N = 65; respiratory or mediastinal: N = 46; > 92% patients had metastatic cancer. Former analgesics: not reported Tapendatol: N = 168, 90 men and 78 women, mean age (SD) = 65.5 (11.21) years, 111 Japanese and 57 Korean. Primary tumour: gastrointestinal: N = 70; respiratory or mediastinal: N = 53; > 92% patients had metastatic cancer. Former analgesics: not reported Inclusion criteria: Patients aged ≥ 20 years with a diagnosis of any type of cancer, experiencing chronic malignant tumour-related pain, with an average pain intensity score over the past 24 hours ≥ 4 on an 11-point numerical rating scale (NRS) (0 = 'no pain' to 10 = 'pain as bad as you can imagine') on the day of randomisation, who "had not taken opioid analgesics (except for codeine phosphate (≤ 60 mg/day), or dihydrocodeine phosphate (≤ 30 mg/day) as antitussives) within 28 days before screening. Patients must have been dissatisfied with the pain relief achieved on their current analgesic treatment for cancer pain and must have had pain requiring treatment with an opioid analgesic (based on the investigator's assessment)." Exclusion criteria: "an uncontrolled or clinically significant arrhythmia; a history of or current disease that could result in increased intracranial pressure, disturbance of consciousness, lethargy, or respiratory problems; any disease for which opioids are contraindicated; a history of surgery intended for the cure of the primary disease or for the treatment of cancer pain within 28 days before screening or during the study; radiation therapy within 7 days before screening; or a psychiatric disorder or concurrent symptoms with accompanying pain that could interfere with efficacy and safety evaluations. Patients were also excluded if they had any of the following laboratory values at screening: white blood cell count ≤ 3000/mL, platelet count ≤ 10 x 10^4/uL, haemoglobin ≤ 9.5 g/dL, corrected total serum calcium level > 12.5 mg/dL, alanine aminotransferase or aspartate aminotransferase ≥ 3 times the upper limit of normal, total bilirubin ≥ 1.5 times the upper limit of normal, or creatinine ≥ 2 mg/dL. The following medications were prohibited: opioid analgesics (including codeine phosphate and dihydrocodeine phosphate as antitussives), except morphine IR 5 mg as rescue medication); opioid antagonists (e.g., naloxone, levallorphan), except for the treatment of respiratory depression; antiparkinsonian drugs; neuroleptics (including antipsychotics, except for prochlorperazine) ; monoamine oxidase inhibitors; serotonin norepinephrine reuptake inhibitors; nora-

	drenergic and specific serotonergic antidepressants; radiotherapy; nerve block; stimulation analgesia; other investigational drugs. The following drugs were prohibited on an as-needed basis as newly started treatment (but could be continued at the same and regimen if started before study entry): Selective serotonin reuptake inhibitors; tricyclic or tetracyclic antidepressants; anti-anxiety agents (e.g., benzodiazepines); hypnotics (e.g., benzodiazepines, non-benzodiazepine hypnotics, barbiturates); anticonvulsants; central muscle relaxants; bisphosphonates; corticosteroids; anti-arrhythmics; non-opioid analgesics (nonsteroidal anti-inflammatory drugs (e.g., cyclo-oxygenase II inhibitors)); pyrazolone antipyretic agents (e.g., sulpyrine) and analine antipyretic agents (e.g., acetaminophen) ; neurotropin; pregabalin. The following were permitted as needed during the study: topical corticosteroids; lidocaine (as a local anesthetic); acetaminophen ($\leq$ 1.5 g/day (Japan) or $\leq$ 4 g/day (Korea) for fever reduction); supportive therapy for chemotherapy; stable doses of very short-acting, non-benzodiazepine hypnotic drugs (for insomnia); medications for nausea, vomiting, and constipation; and rescue medication (as described below). Chemotherapy could be continued at the same dose or chemotherapy doses could be reduced, discontinued, or restarted (if deemed necessary by the investigator); however, if a patient's chemotherapy was considered by the investigator to be interfering with efficacy or safety evaluations of the study drug, that patient was excluded from the study."
Interventions	Oxycodone arm - Drug: Oxycodone HCI - Dose/dosing: 5 to 40 mg bid. The median of the mean total daily dose = 13.8 mg. The median modal (or most frequently used) total daily dose = 10 mg - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: "4 week double-blind treatment period (including titration and maintenance periods), and a 1 week post-treatment period." Median duration of treatment = 28 days - Titration schedule: "Study treatment was initiated with twice daily doses of oxycodone HCl CR 5 mg. During the titration period, doses of study treatment could be increased if necessary to achieve adequate pain control to a maximum of oxycodone HCl CR 40 mg bid after a patient had received the same dose at least four consecutive times. Dose escalations could begin on Day 3 of the titration period. Although not required for dose escalation, the following criteria were evaluated in patients who needed a dose escalation (based on the investigators assessment): 24 hour pain intensity score (11-point NRS) of at least 4 on the previous evaluation and rescue medication used for breakthrough pain at least three times per day. Doses could be decreased during the study as needed for safety reasons to the minimum doses of oxycodone HCl CR (5 mg bid). Study drug doses were titrated to each patient's optimal dose, balancing efficacy and tolerability, until sufficient analgesia was attained. Patients with a pain intensity score of no more than 3 who did not take rescue medication more than twice a day while taking stable doses of study drug (six consecutive identical doses) over a consecutive 3 day period were considered eligible to formally enter the maintenance period; patients who did not meet these criteria were permitted to continue in the double-blind treatment period while continuing to titrate their dose. During the maintenance period, patients continued taking the optimal dose of study drug determined during the titration period. Dose adjustments were permitted during the maintenance period except during the last 3 days. Dose levels during the last 3 days of the maintenance period were to be kept stable."

	- Rescue medication: "Oral morphine IR 5 mg was permitted throughout the study (except during the screening period) as rescue medication for breakthrough pain, with no limit on the number and timing of doses per day." The mean (SD) of the average number of morphine IR doses taken per day = 1.4 (0.43); mean (SD) of the average total daily dose = 6.7 (2.15) mg morphine IR - Other medication: See the inclusion and exclusion criteria in cell above Comparison arm - Drug: Tapentadol - Dose and dosing: 25 to 200 mg bid. The median of the mean total daily dose = 64.5 mg. The median modal (or most frequently used) total daily dose = 50 mg - Formulation: Extended-release - Route of administration: Oral - Length of treatment: "4 week double-blind treatment period (including titration and maintenance periods), and a 1 week post-treatment period." Median duration of treatment = 28 days - Titration schedule: "Study treatment was initiated with twice daily doses of tapentadol ER 25 mg. During the titration period, doses of study treatment could be increased if necessary to achieve adequate pain control to a maximum of tapentadol ER 200 mg bid after a patient had received the same dose at least four consecutive times. Dose escalations could begin on Day 3 of the titration period. Although not required for dose escalation, the following criteria were evaluated in patients who needed a dose escalation (based on the investigators assessment): 24 hour pain intensity score (11 point NRS) of at least 4 on the previous evaluation and rescue medication used for breakthrough pain at least three times per day. Doses could be decreased during the study as needed for safety reasons to the minimum doses of tapentadol ER (25 mg bid). Study drug doses were titrated to each patient's optimal dose, balancing efficacy and tolerability, until sufficient analgesia was attained. Patients with a pain intensity score of no more than 3 who did not take rescue medication more than twice a day while taking stable doses of study drug (six consecutive identical doses) over a consecutive 3 day period were considered eligible to formally enter the maintenance period; patients who did not meet these criteria were permitted to continue in the double-blind treatment period while continuing to titrate their dose. During the maintenance period, patients continued taking the optimal dose of study drug determined during the titration period. Dose adjustments were permitted during the maintenance period except during the last 3 days. Dose levels during the last 3 days of the maintenance period were to be kept stable." - Rescue medication: "Oral morphine IR 5 mg was permitted throughout the study (except during the screening period) as rescue medication for breakthrough pain, with no limit on the number and timing of doses per day." The mean (SD) of the average number of morphine IR doses taken per day = 1.4 (0.46); mean (SD) of the average total daily dose = 7 (2.3) mg morphine IR - Other medication: See the inclusion and exclusion criteria in cell above
Outcomes	- Pain intensity: Assessed by patients once daily (evening on an 11-point numerical rating scale from 0 (no pain) to 10 (= pain as bad as you can imagine). Primary efficacy endpoint was the mean change in average pain intensity from baseline to the last 3 days of study - Patient global impression of change: Questionnaire completed at weeks 1, 2, 3 of double-blind treatment and at the end of study or early withdrawal. Patients rated their overall condition on a scale from 1 (= very much improved) to 7 (= very much worse) by completing the following statement "Since the start of this treatment, my cancer-related pain overall is..."

	- Adverse events: Monitored and coded using the Medical Dictionary for Regulatory Activities. EAch instance of disease progression was considered an adverse event and included in the analysis of treatment-emergent adverse events
Notes	- Study free of commercial funding? No, the study was funded by Janssen Research and Development - Groups comparable at baseline? The groups appear to be comparable at baseline - ITT analyses undertaken? No, the analyses were per protocol (= "a subset of the full analysis population that excluded any patient with a major protocol deviation from a predefined list of deviations")

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patient assignments to study treatment were based on a computer-generated randomization schedule prepared by the sponsor prior to the study; randomization was balanced using randomly permuted blocks and stratified by study site. An Interactive Voice Response System (IVRS) assigned each patient a unique treatment code, which determined that patient's treatment assignment."
Allocation concealment (selection bias)	Low risk	See cell above
Blinding of participants and personnel (performance bias) Pain	Low risk	"The blind was not broken until all patients completed the study and the database was finalized, except in case of emergency."
Blinding of participants and personnel (performance bias) Adverse events	Low risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Low risk	See cell above
Blinding of outcome assessment (detection bias) Adverse events	Low risk	See cell above
Incomplete outcome data (attrition bias) Pain	High risk	Per protocol analyses including 139/172 oxycodone patients and 126/168 tapentadol patients

Imanaka 2013 (*Continued*)

Incomplete outcome data (attrition bias) Adverse events	Low risk	The safety population included all randomized patients who received at least one dose of study drug, that is 340/343 randomised patients (172 oxycodone patients and 168 tapentadol patients)
Selective reporting (reporting bias)	Low risk	All main expected outcomes are reported
Other bias	Low risk	The study does not appear to be subject to high risk of other biases
Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated
For cross-over trials: Are data available for both time periods?	Unclear risk	Not applicable

Kalso 1990

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: Finland
Participants	Patients: 20 patients entered, 19 patients analysed (1 patient excluded as her morphine dose had to be considerably reduced due to side effects); 11 females, 9 males; median age (range): 56 (20-75) years; cancer type: pancreatic (3), breast (5), prostate (1), gastric (1), rectal (2), other (8): cancer stage: metastatic; type of pain: visceral (6), nerve (7), bone (5) , bone-fracture (1), bone-nerve (1), soft tissue (1); setting: Not reported, tertiary?; previous analgesic medication: Buprenorphine (7), oxycodone (1), dextropropoxyphene (1) , aspirin + codeine (1), ibuprophene + buprenorphene (2), indomethacine + buprenorphene (1), dextropropoxyphene + buprenorphene (1), diclophenac + buprenorphine (1) , indomethacine + codeine (2), naproxyn + dextropropoxyphene (1), noramidopyrin + pitofenon (1), ketoprofen + dextropropoxyphene (1) Inclusion criteria: "Twenty patients, 11 women and nine men, who had metastasised cancer and severe pain and who required a change from weaker narcotic analgesic agents (codeine, dextropropoxyphene, buprenorphine) to morphine, participated in the study. " Exclusion criteria: None reported
Interventions	Oxycodone arm - Drug: Oxycodone hydrocloride - Dose and dosing: Previous opioid treatment was discontinued 12 to 24 hours before commencing the study, and during this time 1 mg/kg meperidine was given intramuscularly when requested. The patients titrated themselves free from pain in 48 hours using a patient-controlled analgesia (PCA) device. The concentration of both morphine hydrochloride and oxycodone hydrocloride was 10 mg/ml.This treatment was continued for another 48 hours with the use of the same drug, which was now taken orally. The oral dose was calculated from the IV consumption during the previous 24 hours. The

	daily oral dose was calculated in ml by assuming that the bioavailability of morphine was either 44% (first 10 patients, group 1) or 33% (last 10 patients, group 2) and that the bioavailability of oxycodone hydrocloride was 66% (group 1) and 50% (group 2). To overcome the differences in bioavailabilities of the two drugs, the concentrations of the oral solutions were 2.7 mg/ml for oxycodone hydrocloride and 4 mg/ml for morphine. The dosing interval was 4 hours and the dose was increased by 1 ml at a time if the patient was not pain free during the 4-hour period. If the patient was pain-free, but too sedated, the dose was decreased by 1 ml. PCA device: The bolus dose was 3 mg, which was given over a period of 60 seconds, followed by a tail dose of 2 mg over 1 hour. The lockout time, during which the patient was unable to initiate another dose, was 15 minutes. If the patient was not free from pain with this regimen, the tail dose was increased by 2 mg at a time - Formulation: Immediate-release (oral) - Route of administration: IV (2 days) then oral (2 days) - Length of treatment: 4 days - Titration schedule: See 'Dose and dosing' section above - Rescue medication: See 'Dose and dosing' above. No further information was reported - Other medication: Any pre-existing treatment with non-steroidal anti-inflammatory drings was continued Comparison arm: Same as oxycodone arm, just replacing oxycodone with morphine - For cross-over trials, cross-over schedule: "The same protocol was then repeated with the other drug for another 96 hours"
Outcomes	- Pain severity: Assessed by patient at study start and every 4 hours from 8 am to 8 pm; VAS from 0 to 10 - Side effects: Determined by questioning (have you had nausea, constipation, drowsiness, sedation symptoms, hallucinations, or any other symptoms you would connect with the analgesic?) scored according to grade (moderate = 1, severe = 2); registered on the second day of each study period - Sleep quality, registered on the second day of each study period - Patient preference or acceptability with reason The last 24 hours of each of the four study stages were considered as the steady state and the drug consumptions, and the ratings from the VAS during this period were used for the statistical calculations
Notes	- Study free of commercial funding? Yes. Supported by the Paolo (non-profit) Foundation, Helsinki, Finland - Groups comparable at baseline? No patient details reported by initial treatment allocation - ITT analyses undertaken? No, the data from 1 patient in regard to morphine consumption was excluded as her morphine dose had to be considerably reduced due to side effects. Her data was included in the patient preference analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomised. No further information provided

Kalso 1990 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	See cell above
Blinding of participants and personnel (performance bias) Pain	Unclear risk	The study is described as "double-blind". No further information reported, so it is unclear who was blinded and whether it was adequately executed
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Unclear risk	See cell above
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	See cell above
Incomplete outcome data (attrition bias) Pain	Low risk	The data from 1/20 patients were excluded
Incomplete outcome data (attrition bias) Adverse events	Low risk	Think the data from 1/20 patients were excluded
Selective reporting (reporting bias)	Low risk	The main expected outcomes are reported
Other bias	Low risk	The authors report that "The order in which the drugs were given (either as the first or the second study drug) had no effect on the drug consumption." No other potential biases were identified
Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated
For cross-over trials: Are data available for both time periods?	Low risk	Yes, data are available for both study periods for 19/20 patients

Kaplan 1998

Methods	Design: Randomised, double-blind, parallel-group trial Year: Not reported Country: USA
Participants	Patients: 180 patients enrolled (108 before protocol amendment allowing dose titration before randomisation and 72 after the amendment; 16 of the 72 patients discontinued before randomisation due to lack of acceptable pain control (N = 6), intercurrent illness

	(N = 4), adverse event (N = 2), death (N = 1), withdrawal of consent (N = 1), other (N = 2). 164 patients were randomised (controlled-release oxycodone : N = 81; immediate-release oxycodone: N = 83); N = 156 were included in efficacy analyses (4 patients did not receive the study medication, 3 patients did not complete the efficacy ratings and 1 patient may have received unblinded treatment). All 160 patients who received at least one dose of study medication were included in the safety analyses (of adverse events). 74% of patients were white; mean (SE) age = 59 (1) years; 58% were male; most patients were receiving oral morphine at study entry; cancer type: gastrointestinal (22%), lung (21%), prostate (17%), breast (10%), gynaecological (10%): predominant pain sites were bone and viscera, with an additional 15 patients (9 in controlled-release oxycodone group and 6 in the immediate-release oxycodone group) reporting neuropathic pain Inclusion criteria: "Male and female patients with cancer-related pain were enrolled at 17 centers. The study received institutional review board approval at each center and all patients gave written informed consent. At the time of enrollment, patients were being treated with a strong single-entity opioid or 10 or more tablets per day of a fixed-dose opioid/nonopioid analgesic; were receiving a stable opioid dose; and had stable coexistent disease. Under the original protocol, patients were excluded if they were receiving any other analgesics (opioid or nonopioid) or if they were to receive radiotherapy immediately before enrollment or during the study period. After the study had begun, these exclusion criteria were eliminated by an amendment to facilitate enrollment into the study, which had been slow." Exclusion criteria: See above
Interventions	Oxycodone arm - Drug: Oxycodone - Dose/dosing: Oxycodone tablets (10 mg) every 12 hours (8 am and 8 pm) and placebo tablets every 2 pm and bedtime. Mean daily dose (range) = 114 (20 to 400) mg - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 6 days - Titration schedule: The original study design did not allow dose titration or use of rescue medication for breakthrough/incident pain. Patients whose pain was not effectively controlled at the initial oxycodone dose calculated from previous opioid use were discontinued from the study. However, an interim analysis conducted to determine whether dose adjustments were required showed that drop-out rates were too high for relevant conclusions. This suggested that the initial conversion dose estimate was not adequate for a subgroup of patients, and the protocol was amended to include open-label titration with immediate-release oxycodone before the patients were randomised to double-blind treatment, as well as the use of immediate-release oxycodone 5 mg tablets as rescue medication throughout the trial. Supplemental doses could be taken no more frequently than every 4 hours at no more than approximately 1/6 of the daily dose of study medication. No further information was reported - Rescue medication: See 'Titration schedule' above. Mean number of rescue medication doses per day = 0.6 - Other medication: See 'Inclusion criteria' above. No further information reported Comparison arm - Drug: Oxycodone - Dose and dosing: Oxycodone tablets (5 mg) every 6 hours (8 pm, bedtime ($\geq$ 3 hours after 8 pm, but not after 2 am), 8 am and 2 pm). Mean daily dose (range) = 127 (40 to

	640) mg - Formulation: Immediate-release - Route of administration: Oral - Length of treatment: 6 days - Titration schedule: The original study design did not allow dose titration or use of rescue medication for breakthrough/incident pain. Patients whose pain was not effectively controlled at the initial oxycodone dose calculated from previous opioid use were discontinued from the study. However, an interim analysis conducted to determine whether dose adjustments were required showed that drop-out rates were too high for relevant conclusions. This suggested that the initial conversion dose estimate was not adequate for a subgroup of patients, and the protocol was amended to include open-label titration with immediate-release oxycodone before the patients were randomised to double-blind treatment, as well as the use of immediate-release oxycodone 5 mg tablets as rescue medication throughout the trial. Supplemental doses could be taken no more frequently than every 4 hours at no more than approximately 1/6 of the daily dose of study medication. No further information was reported - Rescue medication: See 'Titration schedule' above. Mean number of rescue medication doses per day = 1 - Other medication: See 'Inclusion criteria' above. No further information reported
Outcomes	- Pain intensity: Assessed by patient at study start and 4 times daily at 8 am, 2 pm, 8 pm and bedtime; categorical verbal scale from 0 (= none, 1 = slight, 2 = moderate) to 3 (= severe) - Acceptability of treatment: Assessed by patient at study start and twice daily at 8am and 8 pm; categorical verbal scale from 1 (= very poor; 2 = poor, 3 = fair, 4 = good) to 5 (= excellent) - Adverse events: Those spontaneously reported by patients or observed by investigators were recorded, and their severity and relationship to study drug (none, possible, probable, definite) were assessed by each investigator
Notes	- Study free of commercial funding? No, some or one of the authors (including the corresponding author) are or is employee(s) of Purdue Pharma Ltd, the manufacturer of the study drugs - Groups comparable at baseline? The authors report "There were no significant differences in the primary pain site, prestudy opioid, or cancer diagnosis between the two treatment groups". No other information reported - ITT analyses undertaken? No, 156 and 160/164 patients, respectively, were included in the safety and efficacy analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The authors state that the patients were randomised, but give no further details
Allocation concealment (selection bias)	Unclear risk	The authors state that the patients were randomised, but give no further details

Kaplan 1998 (*Continued*)

Blinding of participants and personnel (performance bias) Pain	Low risk	Double-blind placebo-controlled study. To maintain the blind, all doses of the study medication were encapsulated in green size #00 lactose-filled capsules
Blinding of participants and personnel (performance bias) Adverse events	Low risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Low risk	See cell above
Blinding of outcome assessment (detection bias) Adverse events	Low risk	See cell above
Incomplete outcome data (attrition bias) Pain	Low risk	A total of 156/164 patients were included in the efficacy analyses
Incomplete outcome data (attrition bias) Adverse events	Low risk	A total of 160/164 patients were included in the safety analyses
Selective reporting (reporting bias)	Low risk	All obvious outcomes are reported
Other bias	Low risk	The study does not appear to be subject to high risk of other biases
Were the patients adequately titrated?	High risk	No before amendment, unclear after amendment
For cross-over trials: Are data available for both time periods?	Unclear risk	Not applicable

Lauretti 2003

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: Brazil
Participants	Patients: 22/26 enrolled patients were evaluated (withdrawals due to death (unrelated to the study, N = 1), uncontrollable nausea/vomiting (N = 1), and unstable pain control requiring spinal drugs (N = 2)); mean/median (?) (SD/inter-quartile range?) age = 59 (19) years; 15 males/7 females; cancer type: oropharynx (N = 9), lung (N = 3), prostate gland (N = 2), colon (N = 4), gastric (N = 2), ovary (N = 2); pain types were somatic and visceral; adjuvant therapy: radiation (N = 1), chemotherapy (N = 6), radiation/ chemotherapy (N = 4), none (N = 11) Inclusion criteria: "26 patients with chronic cancer pain of the visceral and somatic type.

	.... Before enrolling in this actual study, patients received 3-4mg/kg^{-1} tramadol, plus nonsteroidal anti-inflammatory drugs: however they still complained of pain VAS $\geq$ 4 cm" Exclusion criteria: None listed
Interventions	Oxycodone arm - Drug: Oxycodone - Dose/dosing: The optimum dosage was calculated on a daily basis, and the consumption ratio of oxycodone to morphine was set at 1:1.8 - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 14 days - Titration schedule: The study started with an open-label, randomised titration phase to achieve stable pain control for 7 days. Patients only used immediate-release morphine and had free access to it to keep pain VAS < 4 - Rescue medication: At any point, patients were allowed to use immediate-release morphine (10 mg tablets) as needed to keep pain VAS $\leq$ 4 - Other medication: As part of the protocol, all patients were taking oral 25 mg amitriptyline at bedtime Comparison arm - Drug: Morphine - Dose/dosing: The optimum dosage was calculated on a daily basis, and the consumption ratio of oxycodone to morphine was set at 1:1.8 - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 14 days - Titration schedule: The study started with an open-label, randomised titration phase to achieve stable pain control for 7 days. Patients only used immediate-release morphine and had free access to it to keep pain VAS < 4 - Rescue medication: At any point, patients were allowed to use immediate-release morphine (10 mg tablets) as needed to keep pain VAS $\leq$ 4 - Other medication: As part of the protocol, all patients were taking oral 25 mg amitriptyline at bedtime - For cross-over trials, cross-over schedule: "After stable pain relief was achieved [during titration phase], this was followed by a double-blind, cross-over phase in two periods, 14 days each..... and no period of washout was was allowed for ethical reasons"
Outcomes	- Pain intensity: Assessed by patients; 10 cm VAS from 0 (= no pain at all) to 10 (= worst possible pain) - Patient satisfaction: Assessed by patient - Adverse events: Assessed by patient (possibly using a 10 cm VAS similar to pain intensity, but data not reported that way) - Number of rescue morphine tablets: Assessed by patient It also appears that an investigator recorded these data on a weekly basis
Notes	- Study free of commercial funding? No information reported - Groups comparable at baseline? Unclear, no information reported - ITT analyses undertaken? No, 22/26 patients were included in the analyses

Lauretti 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) Pain	Low risk	The patients were blinded, but it is unclear whether the investigator administering the drugs was
Blinding of participants and personnel (performance bias) Adverse events	Low risk	The patients were blinded, but it is unclear whether the investigator administering the drugs was
Blinding of outcome assessment (detection bias) Pain	Low risk	The patients and outcome assessor were blinded
Blinding of outcome assessment (detection bias) Adverse events	Low risk	The patients and outcome assessor were blinded
Incomplete outcome data (attrition bias) Pain	Unclear risk	Data from 22/26 patients included
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Data from 22/26 patients included
Selective reporting (reporting bias)	High risk	All obvious outcomes are reported, although not in the most useful manner (e.g., no collapsing across study phase weeks, that is, mean final weekly dose of CR oxycodone and morphine are reported for 4 weeks, not 2 weeks)
Other bias	Low risk	It is unclear whether there were any carryover effects, but there probably were none
Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated
For cross-over trials: Are data available for both time periods?	Low risk	Yes, data are available from both time periods, although not reported by arm (see two cells above)

Leow 1995

Methods	Design: Randomised, open-label, single-dose, cross-over trial Year: Not reported Country: Australia
Participants	Patients: 12 patients entered; 5 females, 7 males; mean age (SD): 68.8 (12.6) years; cancer type: cervical (2), breast (1), prostate (1), bowel (1), anal (1), endometrial (1), renal (1), lung/bronchial (2), skeletal or thoracic-vertedral metastases (2); all inpatients; all receiving oral nutrition; none hypovolemic; all opioid-naive apart from 1 patient who was receiving paracetamol + dextropropoxyphene. Two patients had compromised renal function, and 5 patients had impaired liver function to varying degree Inclusion criteria: Inpatients with moderate to severe cancer pain Exclusion criteria: Known hypersensitivity to oxycodone or other opioid analgesics and/or a history of drug dependence
Interventions	Oxycodone arm - Drug: Oxycodone hydrocloride - Dose and dosing: Single dose of IV oxycodone hydrochloride in a concentration of 5 mg/ml, equivalent to 4.5 mg/ml oxycodone base. The mean (SD) IV oxycodone dose administered was 0.11 (0.02) mg/kg (range 5.4 to 9 mg), which a previous study by the authors had shown to produce satisfactory analgesia in patients with moderate to severe cancer. Patients with impaired liver function received the lower doses of IV oxycodone. The IV oxycodone dose was administered into a forearm vein. The rate of injection (0.5 to 5 min) was titrated by the anaesthetist - Formulation: IV - Route of administration: IV - Length of treatment: 24 hours, 1 dose - Titration schedule: See 'Dose and dosing' section above - Rescue medication: Oral paracetamol (up to 1 g every 4 hours) or Di-Gesic (up to 2 tablets every 4 hours) were available as rescue medication on patient request. Nine patients asked for supplementary analgesics after 4 hours post-dosing - Other medication: "Medications that had been taken routinely by patients before the study, were permitted." Comparison arm - Drug: Oxycodone - Dose and dosing: Single dose of 30 mg oxycodone base in a rectal suppository - Formulation: Suppository - Route of administration: Rectal - Length of treatment: 24 hours, 1 dose - Titration schedule: See 'Dose and dosing' section above - Rescue medication: Oral paracetamol (up to 1 g every 4 hours) or digesic (up to 2 tablets every 4 hours) were available as rescue medication on patient request. Nine patients asked for supplementary analgesics after 6 to 8 hours post-dosing - Other medication: "Medications that had been taken routinely by patients before the study, were permitted." - For cross-over trials, cross-over schedule: "Patients were randomly assigned to begin treatment with either a single dose of.... The second treatment was administered 24 h after the first dose."

Outcomes	- Pain intensity: Assessed by patient at study start at 0.5, 1, 2, 4, 8, 12 and 24 hours post-dosing; 10 cm VAS with delimiters 'no pain' and 'worst pain imaginable' - Side effects: Assessed by questioning the patient at study start at 0.5, 1, 2, 4, 8, 12 and 24 hours post-dosing; Patients were asked to report any side effects, but were specifically asked whether they experienced nausea, vomiting, pruritus, lightheadedness, or drowsiness, using a 4-point verbal rating scale going from 0 to 3 (none = 0, mild = 1, moderate = 3, severe = 3)
Notes	- Study free of commercial funding? No. Supported by the Boots Company (Australia; manufacturer of the rectal suppository study drug), Pty Ltd, the University of Queensland Cancer Research Fund, and the Queensland Cancer Fund - Groups comparable at baseline? No patient details reported by initial treatment allocation - ITT analyses undertaken? It appears so. It is not possible to confirm it based on the presented date, but no information to the contrary is reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to begin treatment with..." No further information reported
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned to begin treatment with..." No further information reported
Blinding of participants and personnel (performance bias) Pain	High risk	The study was open-label
Blinding of participants and personnel (performance bias) Adverse events	High risk	The study was open-label
Blinding of outcome assessment (detection bias) Pain	High risk	The study was open-label
Blinding of outcome assessment (detection bias) Adverse events	High risk	The study was open-label
Incomplete outcome data (attrition bias) Pain	Low risk	All data appear to be included. It is not possible to confirm it based on the presented data, but no information to the contrary is reported

Incomplete outcome data (attrition bias) Adverse events	Low risk	All data appear to be included. It is not possible to confirm it based on the presented data, but no information to the contrary is reported
Selective reporting (reporting bias)	Low risk	All expected outcomes seem to be reported
Other bias	Low risk	"An absence of carryover effects (P > 0.05) between Treatments 1 and 2 was confirmed using the Grizzle analysis for cross-over designs"
Were the patients adequately titrated?	Unclear risk	Not enough information reported
For cross-over trials: Are data available for both time periods?	Low risk	Yes, data are available from both time periods

Mercadante 2010

Methods	Design: Randomised, parallel group trial Year: Not reported Country: Italy
Participants	Patients: 60 patients randomised; 46/60 patients completed baseline evaluation (21 patients in group oxycodone and 25 patients in group morphine, 14/60 patients did not complete baseline evaluation as they were lost to follow up); 27 females, 19 males; mean age (SD): 63.2 (9.48) years. 19 oxycodone and 20 morphine patients completed 4 weeks of study participation and 7 and 10 patients, respectively, completed 8 weeks of study participation Inclusion criteria: Patients with pancreatic cancer with local disease, presenting abdominal pain with an intensity ≥ 4/10 numerical rating scale from 0 to 10, and no longer responsive no nonopioid analgesics Exclusion criteria: Distant and bone metastases, or prevalent somatic pain due to evident peritoneal involvement, changes in chemotherapy regimen, hepatic or renal failure, cognitive failure, lack of cooperation, aged < 18 or > 80 years, and a Karnofsky performance status < 50
Interventions	Oxycodone arm - Drug: Oxycodone - Dose and dosing: Starting dose of 20 mg/day, according to an approximate morphine: oxycodone ratio of 1.5:1. For patients requiring an increase in the dose for increasing pain (> 4/10 or > 3 breakthrough pain medications per day) during the study period, opioid doses were increased according to the clinical needs. Mean dose (SD) at week 1: 23.8 (8) mg/day; mean dose (SD) at week 2: 25.5 (8) mg/day; mean dose (SD) at week 3: 27.9 (9) mg/day; Mean dose (SD) at week 4: 33.1 (14) mg/day; mean dose (SD) at week 8: 45.7 (24) mg/day - Formulation: Sustained-release - Route of administration: Oral

	- Length of treatment: 4 weeks (with a study extension up to 8 weeks) - Titration schedule: "Patients were recruited and followed during admission to the palliative care unit, as outpatients and at home. Physicians provided frequent call contacts to adjust the opioid dose at any time". See also 'Dose and dosing' section above. No further information provided - Rescue medication: Oral morphine in doses of 1/6 of the daily dose was provided (starting at 5 mg initially) - Other medication: "Adjuvants and symptomatic drugs were prescribed as indicated by the clinical situation." Comparison arm - Drug: Morphine - Dose and dosing: Starting dose of 30 mg/day, according to an approximate morphine: oxycodone ratio of 1.5:1. For patients requiring an increase in the dose for increasing pain (> 4/10 or > 3 breakthrough pain medications per day) during the study period, opioid doses were increased according to the clinical needs. Mean dose (SD) at week 1: 35 (9) mg/day; mean dose (SD) at week 2: 36.2 (14) mg/day; mean dose (SD) at week 3: 41 (19) mg/day; mean dose (SD) at week 4: 42.6 (21) mg/day; mean dose (SD) at week 8: 60 (46) mg/day - Formulation: Sustained-release - Route of administration: Oral - Length of treatment: 4 week (with a study extension up to 8 weeks) - Titration schedule: "Patients were recruited and followed during admission to the palliative care unit, as outpatients and at home. Physicians provided frequent call contacts to adjust the opioid dose at any time". See also 'Dose and dosing' section above. No further information provided - Rescue medication: Oral morphine in doses of 1/6 of the daily dose was provided (starting at 5 mg initially) - Other medication: "Adjuvants and symptomatic drugs were prescribed as indicated by the clinical situation."
Outcomes	- Pain intensity (average in the last 24 hours): Assessed by patient, using a numerical rating scale from 0 to 10 - Opioid-related symptoms (including nausea and vomiting, drowsiness and confusion) : Assessed by patient, using a categorical scale from 0 (= absent, 1 = slight, 2 = moderate) to 3 (= severe) - Constipation: Assessed by patient, using a categorical scale from 0 (= 1 passage, 1 to 2 days; 1 = 1 passage, 3 to 4 days; 2 = 1 passage, 4 days) to 3 (= only by enema)
Notes	- Study free of commercial funding? Unclear. No details reported - Groups comparable at baseline? No patient details reported by initial treatment allocation - ITT analyses undertaken? No, it does not appear so. From baseline to study end at 4 weeks 11/30 oxycodone patients and 10/30 morphine patients dropped out of the study and only the data from patients who completed the study phases are reported/analysed by week (0, 1, 2, 3, 4, and 8)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	"Patients were randomized by a computer system in 2 groups." No further information reported
Allocation concealment (selection bias)	Unclear risk	See cell above
Blinding of participants and personnel (performance bias) Pain	High risk	Unblinded study
Blinding of participants and personnel (performance bias) Adverse events	High risk	Unblinded study
Blinding of outcome assessment (detection bias) Pain	High risk	Unblinded study
Blinding of outcome assessment (detection bias) Adverse events	High risk	Unblinded study
Incomplete outcome data (attrition bias) Pain	High risk	From baseline to study end at 4 weeks 11/30 oxycodone patients and 10/30 morphine patients dropped out of the study and only the data from patients who completed the study phases are reported/analysed by week (0, 1, 2, 3, 4, and 8)
Incomplete outcome data (attrition bias) Adverse events	High risk	From baseline to study end at 4 weeks 11/30 oxycodone patients and 10/30 morphine patients dropped out of the study and only the data from patients who completed the study phases are reported/analysed by week (0, 1, 2, 3, 4, and 8)
Selective reporting (reporting bias)	Low risk	All obvious outcomes appear to be reported
Other bias	Low risk	The study does not appear to be subject to high risk of other biases
Were the patients adequately titrated?	Unclear risk	Not enough information reported
For cross-over trials: Are data available for both time periods?	Unclear risk	Not applicable

Mucci-LoRusso 1998

Methods	Design: Randomised, parallel group trial Year: Not reported Country: USA
Participants	Patients: 101 patients randomised; 100/101 patients received ≥ one dose of study medication; N = 48 in oxycodone group and 52 in the morphine group, 55% patients were male, mean (range) age = 59 (30 to 83) years; bone and viscera were most common pain sites; nerve pain was the primary pain type in 10/48 oxycodone and 9/52 morphine patients; most common pre-study pain medication was fixed-dose oxycodone-acetaminophen combination (22 patients in each group), followed by single-entity morphine (13 oxycodone and 17 morphine patients). Most patients were receiving > 1 pain medication pre-study and all but 3 patients (all in the oxycodone group) were receiving opioids prior to enrolment, the mean (range) oral oxycodone equivalent of the pre-study dose = 64 (14 to 280) mg in the oxycodone group and 70 (14-235) mg in the morphine group. 7 oxycodone and 9 morphine patients discontinued the study before achieving stable pain control due to adverse experiences (2 oxycodone and 6 morphine patients), intercurrent illness (3 oxycodone patients), ineffective treatment (1 oxycodone and 1 morphine patients), patient request (1 oxycodone and 1 morphine patients), and protocol violation (1 morphine patient). An additional 4 patients dropped out of the study after achieving stable pain control due to adverse experience (1 oxycodone patient) , protocol violation (1 oxycodone patient), intercurrent illness (1 morphine patient) and worsening of pre-existing condition (1 morphine patient) Inclusion criteria: Patients who required around-the-clock treatment with opioid analgesics for chronic cancer-related pain with the equivalent of 30 to 340 mg of oral oxycodone daily. Patients whose pain was not controlled by maximum recommended doses of nonopioid analgesics were also eligible if they would require ≥ 30 mg Exclusion criteria: "a history of sensitivity to oxycodone or morphine, any contra-indication for opioid therapy (such as paralytic ileus or severe pulmonary disease) or severely compromised organ function that could obscure efficacy or or adversely affect safety. Patients whose pain control was so fragile they could not switch opioids were also excluded. "
Interventions	Oxycodone arm - Drug: Oxycodone hydrochloride - Dose and dosing: Multiples of 20 mg tablets, every 12 hours (8 am and 8 pm). Starting dose was calculated from the patients' pre-study daily opioid dose and could be adjusted based on the investigator's judgement. The dose was titrated until stable pain control was achieved. Pain control was considered stable when, over a 48-hour period, the every 12 h dose was unchanged, ≤ 2 supplemental analgesic doses were taken per day, the dosing regimen for any non-opioids or adjuvants was unchanged, and the patient reported that pain control was acceptable and any side effects were tolerable. Patients who could not be stabilised within 10 days were discontinued. Mean final daily doses of every 12 h (range): 101 (40 to 360) mg - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: Up to 12 days - Titration schedule: See 'Dose and dosing' section above - Rescue medication: Immediate-release oxycodone in multiples of two 5 mg tablets. Each supplemental medication dose was 1/4 to 1/3 of every 12 h scheduled dose. Patients were instructed to take a supplemental dose as needed for breakthrough pain, but not

	more frequently than once every 2 to 4 hours or 1 hour before activity associated with incident pain. Median dose use on the next to last study day (during stable pain control) = 1 (range 0 to 4) and median dose use on last study day (during stable pain control) = 1 (range 0 to 3) - Other medication: "Non-opioid analgesics and adjuvant medications were allowed during the study provided they had been given on a regular basis (not as needed) before the study." Comparison arm - Drug: Morphine sulfate - Dose and dosing: Multiples of 30 mg tablets, every 12 hours (8 am and 8 pm). Starting dose was calculated from the patients' pre-study daily opioid dose and could be adjusted based on the investigator's judgement. The dose was titrated until stable pain control was achieved. Pain control was considered stable when, over a 48-hour period, the q12h dose was unchanged, ≤ 2 supplemental analgesic doses were taken per day, the dosing regimen for any non-opioids or adjuvants was unchanged, and the patient reported that pain control was acceptable and any side effects were tolerable. Patients who could not be stabilised within 10 days were discontinued. Mean final daily doses every 12 h (range) : 140 (60 to 300) mg - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: Up to 12 days - Titration schedule: See 'Dose and dosing' section above - Rescue medication: Immediate-release morphine in multiples of 15 mg tablets. Each supplemental medication dose was 1/4 to 1/3 of every 12 h scheduled dose. Patients were instructed to take a supplemental dose as needed for breakthrough pain, but not more frequently than once every 2 to 4 hours or 1 hour before activity associated with incident pain. Median dose use on the next to last study day (during stable pain control) = 1 (range 0 to 3) and median dose use on last study day (during stable pain control) = 1 (range 0 to 3) - Other medication: "Non-opioid analgesics and adjuvant medications were allowed during the study provided they had been given on a regular basis (not as needed) before the study."
Outcomes	- Pain intensity (average since previous evaluation): Assessed by patient at baseline and before every q12h dose, using a categorical scale from 0 (= none) (1 = slight, 2 = moderate) to 3 (= severe). Also assessed after ≥ 48 hours of stable pain control using the categorical scale and a 100 mm VAS scale from 0 (= no pain) to 100 (worst possible pain) - Adverse experiences and drug effects: Assessed by patient in a daily diary, and after ≥ 48 hours of stable pain control by using the Specific Drug Effect Questionnaire 100 mm VAS scale (?) from 0 (= not at all) to 100 (an awful lot); also assessed by observers after ≥ 48 hours of stable pain control by using the Specific Drug Effect Questionnaire 100 mm VAS scale (?) from 0 (= not at all) to 100 (extremely) - Drowsiness and nausea: Assessed by patient after ≥ 48 hours of stable pain control (?) , using a categorical scale from 0 (= none, 1 = slight, 2 = moderate) to 3 (= severe) and a 100-mm VAS scale from 0 (= none) to 100 (worst possible) - Acceptability of therapy: Assessed by patient at baseline and study end, using a categorical scale from 1 (= very poor, 2 = poor, 3 = fair, 4 = good) to 5 (= excellent) - Quality of life: Assessed by patient at baseline and study end, using the Functional Assessment of Cancer Therapy-General (FACT-G), a 28-item questionnaire consisting

	of 5 subscales measuring different aspects of quality of life: Physical, social/family, relationship with physician, emotional and functional
Notes	- Study free of commercial funding? No. The authors were either "financially compensated for their efforts" or employees of the study drug manufacturer - Groups comparable at baseline? Unclear. No patient details reported by initial treatment allocation - ITT analyses undertaken? No, 100/101 patients were analysed for safety; 79/101 patients who achieved stable pain control and had simultaneous pharmacokinetic-pharmacodynamicassessments were analysed for efficacy (39 oxycodone, 40 morphine)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Block randomization was used to ensure that all centers had a comparable number of patients in each treatment group." No further information reported
Allocation concealment (selection bias)	Unclear risk	No further information reported than that in the cell above
Blinding of participants and personnel (performance bias) Pain	Low risk	"The double-dummy technique was used to blind the study medications."
Blinding of participants and personnel (performance bias) Adverse events	Low risk	"The double-dummy technique was used to blind the study medications."
Blinding of outcome assessment (detection bias) Pain	Low risk	Patient recorded. See cell above
Blinding of outcome assessment (detection bias) Adverse events	Low risk	See cell above
Incomplete outcome data (attrition bias) Pain	High risk	A total of 79/101 patients who achieved stable pain control and had simultaneous pharmacokinetic-pharmacodynamic assessments were analysed for efficacy
Incomplete outcome data (attrition bias) Adverse events	Low risk	A total of 100/101 patients were analysed for safety
Selective reporting (reporting bias)	Low risk	All obvious outcomes are reported

Mucci-LoRusso 1998 (*Continued*)

Other bias	Low risk	The study does not appear to be subject to high risk of other biases
Were the patients adequately titrated?	Low risk	The patients were adequately titrated
For cross-over trials: Are data available for both time periods?	Unclear risk	Not applicable

Parris 1998

Methods	Design: Randomised, double-blind, parallel group trial Year: Not reported Country: USA
Participants	Patients: 111 patients randomised; 103/111 patients received ≥ one dose of study medication; N = 52 in controlled-release group and 51 in the immediate-release group, 50% patients were female, average (mean?) (range) age = 57 (31 to 80) years; bone (45%) and viscera (28%) were most common pain sites; most common cancer diagnoses were breast, gastrointestinal, lung, and gynaecological. 66/111 patients completed the 5-day study period (33 in each group). Pre-study analgesics: Oxycodone and acetaminophen (71%), most lower-dose patients received a total daily pre-study oxycodone dosage of 30 to 45 mg with 2.0 to 2.9 g of acetaminophen; higher-dose patients received a daily oxycodone dosage of 50 to 60 mg with 3.2 to 3.9 g of acetaminophen; other prior opioids included codeine and acetaminophen (17%), hydrocodone and acetaminophen (10%) , propoxyphene napsylate and acetaminophen (2%), and transdermal fentanyl (1%) (protocol violation). A total of 19 controlled-release and 18 immediate-release patients discontinued the study due to adverse events (4 controlled-release and 7 immediate-release patients), unrelated illness (1 in each group), ineffective treatment (10 controlled-release and 4 immediate-release patients), protocol violation (4 controlled-release and 5 immediate-release patients), and other (1 immediate-release patient) Inclusion criteria: "The study included adult patients recruited from 15 centers in the United States who were receiving 6 to 12 tablets or capsules per day of fixed-combination analgesics for cancer-related pain. Patients were of either gender and had stable coexistent disease." Exclusion criteria: "Patients were excluded if their pain was not already acceptably controlled; if they had surgery or radiotherapy within 10 days of prior to study or anticipated these procedures during study; of they had compromised function of a major organ system; or of they were receiving nonopioid analgesics (before the protocol was amended) . Of course, concomitant nonanalgesic therapies were allowed during the study. To encourage participation and to lower the discontinuation rate, the protocol was modified during the study to include patients undergoing or recently given radiotherapy and those receiving stable doses of nonopioid analgesics or analgesic adjuvants. In addition,. patients receiving ten to more tablets or capsules of fixed-combination analgesics were no longer permitted to enter the study, but could be enrolled in a companion study intended for patients with greater opioid requirements."

Parris 1998 (*Continued*)

Interventions	Oxycodone arm - Drug: Oxycodone - Dose and dosing: 30 mg, every 12 hours, thus total daily dosage = 60 mg. Mean daily dosage = 60 mg (see 'Titration schedule' below) - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 5 days - Titration schedule: Patients needing titration of analgesic or supplemental medication were required to discontinue from the study - Rescue medication: See 'Titration schedule' - Other medication: "See 'Titration schedule'. "Of course, concomitant nonanalgesic therapies were allowed during the study" Comparison arm - Drug: Oxycodone - Dose and dosing: 15 mg, 4 times daily, thus total daily dosage = 60 mg. Mean daily dosage = 60 mg (see 'Titration schedule' below) - Formulation: Immediate-release - Route of administration: Oral - Length of treatment: 5 days - Titration schedule: Patients needing titration of analgesic or supplemental medication were required to discontinue from the study - Rescue medication: See 'Titration schedule' - Other medication: See 'Titration schedule'. "Of course, concomitant nonanalgesic therapies were allowed during the study"
Outcomes	- Pain intensity: Assessed by patient at baseline and 4 times daily, that is, morning (overnight pain rating), midday (morning pain rating), evening (afternoon pain rating), and bedtime (evening pain rating), using a categorical scale from 0 (= none) (1 = slight, 2 = moderate) to 3 (= severe) - Acceptability of current therapy: Assessed by patient at baseline and 2 times daily, that is, for both day and night, using a categorical scale from 1 (= very poor) (2 = poor, 3 = fair, 4 = moderate) to 5 (= excellent) - Adverse experiences: "Observers contacted patients by telephone daily throughout the 5-day study period and recorded information about adverse events and changes in the patients' condition."
Notes	- Study free of commercial funding? No. The study was sponsored by the drug manufacturers (The Purdue Frederick Company and Purdue Pharma L.P.) and some of the authors were employees of the study drug manufacturer - Groups comparable at baseline? No patient details reported by initial treatment allocation - ITT analyses undertaken? Yes, it seems so. 103/111 patients who took $\geq$ 1 study drug dose constituted the ITT population (52 controlled-release, 51 immediate-release), 8/111 patients were excluded for administrative reasons, which are not further specified; 109/111 patients were analysed for safety
Risk of bias	

Parris 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information reported beyond that "This was a randomized, double-blind, parallel-group study"
Allocation concealment (selection bias)	Unclear risk	See cell above
Blinding of participants and personnel (performance bias) Pain	Low risk	"This was a randomized, double-blind, parallel-group study".... "using a double-dummy technique". No further information reported
Blinding of participants and personnel (performance bias) Adverse events	Unclear risk	See cell above. We here assume that the patients were blinded, but it is unclear whether the personnel administering the study medication or the personnel assessing some of the outcomes, or both, were also blinded
Blinding of outcome assessment (detection bias) Pain	Low risk	This outcome was patient-assessed. See cell above
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	See cell above. We here assume that the patients were blinded, but it is unclear whether the personnel administering the study medication and/or the personnel assessing some of the outcomes were also blinded
Incomplete outcome data (attrition bias) Pain	Low risk	A total of 103/111 patients who took $\geq$ 1 study drug dose constituted the ITT population (52 controlled-release, 51 immediate-release), 8/111 patients were excluded for administrative reasons, which are not further specified. The pain data appear to include these 103 patients
Incomplete outcome data (attrition bias) Adverse events	Low risk	A total of 109/111 patients were analysed for safety
Selective reporting (reporting bias)	Low risk	All obvious outcomes appear to be reported
Other bias	Low risk	The study does not appear to be subject to high risk of other biases

Parris 1998 (*Continued*)

Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated because otherwise they were discontinued
For cross-over trials: Are data available for both time periods?	Unclear risk	Not applicable

Riley 2014

Methods	Design: Randomised, double-blind, parallel group trial (with cross-over to other arm for non-responders to first line opioid) Year: 2006 to 2011 Country: UK
Participants	Patients: 200 patients randomised; 198/200 patients received ≥ 1 dose of study medication; N = 100 in the oxycodone group and 98 in the morphine group; 198 were included in the intention-to-treat analyses: - Oxycodone: N = 100; 38 males and 62 females, mean (SD) age = 58.9 (13.2) years; cancer diagnosis: breast (18), lower gastrointestinal (16), upper gastrointestinal (2), pancreas and hepatobiliary (4), sarcoma (8), lung (13), gynaecological (9), urinary tract (3), prostate (8), haematological (7), malignant melanoma (6), head and neck (3), other (3); concomitant opioid medications before randomisation: As required morphine (40), as required oxycodone (3), codeine (45), tramadol (45), dihydrocodeine (5), dextropropoxyphene (1), buprenorphine (3). A total of 20/100 patients who received first line oxycodone withdrew from the trial for drug (16) or trial (4) reasons - Morphine: N = 100; 50 males and 50 females, mean (SD) age = 59.2 (11.6) years; cancer diagnosis: breast (14), lower gastrointestinal (11), upper gastrointestinal (10), pancreas and hepatobiliary (10), sarcoma (11), lung (5), gynaecological (7), urinary tract (12), prostate (2), haematological (6), malignant melanoma (4), head and neck (2), other (6); concomitant opioid medications before randomisation: As required morphine (51), as required oxycodone (1), codeine (47), tramadol (47), dihydrocodeine (3), dextropropoxyphene (0), buprenorphine (0). 13/98 patients who received first line oxycodone withdrew from the trial for drug (10) or trial (3) reasons Inclusion criteria: "Inpatients and outpatients were identified and recruited at a tertiary referral cancer center by the specialist palliative care team. Patients were eligible if they needed to begin a regular oral strong opioid for cancer-related pain and were strong opioid naive, that is, had not taken a regular strong opioid within the previous month. The use of an "as required" strong opioid was permitted (less than six doses in 24 hours). Patients were recruited before, or within 24 hours, of starting a regular strong opioid." Exclusion criteria: Renal impairment (serum creatinine ≥ 1.5 times the upper limit of normal), requirement of parenteral opioids, previous poor response to either morphine or oxycodone, and pregnancy
Interventions	Oxycodone arm - Drug: Oxycodone - Dose and dosing: See 'Titration schedule'. No further information reported - Formulation: Controlled-release - Route of administration: Oral

	- Length of treatment: 1 year - Titration schedule: "Patients were initially titrated on immediate-release preparations, administered at four-hourly intervals with additional as required doses available for breakthrough pain .... the starting dose was determined by the treating physician on an individual patient basis and titrated accordingly.... until adequate pain control was achieved or intolerable side effects were reported by the patient. At this stage, patients were converted to the comparable modified-release preparations. Nonresponders to the first opioid were switched to the alternative opioid. As this was not a stable analgesic setting, the ratio of oral morphine:oxycodone (2:1).... Doses were retitrated according to response." - Rescue medication: See 'Titration schedule' - Other medication: "Adjuvant medications (laxatives, antiemetics, coanalgesics) were either started or continued where indicated." Comparison arm - Drug: Morphine - Dose and dosing: See 'Titration schedule'. No further information reported - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 1 year - Titration schedule: "Patients were initially titrated on immediate-release preparations, administered at four-hourly intervals with additional as required doses available for breakthrough pain .... the starting dose was determined by the treating physician on an individual patient basis and titrated accordingly.... until adequate pain control was achieved or intolerable side effects were reported by the patient. At this stage, patients were converted to the comparable modified-release preparations. Nonresponders to the first opioid were switched to the alternative opioid. As this was not a stable analgesic setting, the ratio of oral morphine:oxycodone (2:1).... Doses were retitrated according to response." - Rescue medication: See 'Titration schedule' - Other medication: "Adjuvant medications (laxatives, antiemetics, coanalgesics) were either started or continued where indicated."
Outcomes	- Pain intensity: Assessed by patient at baseline and daily during titration in addition to the following times: (1) when the patient is clinically stabilised on first line opioid, (2) if the patient does not respond to first-line opioid and requires switching to alternative opioid, (3) when patient is clinically stabilised on second line opioid, (4) if the patient's analgesic requirement have increase by 200% of their initial stable opioid dose, and (5) if the patient does not respond to second line opioid or fits the criteria to exit the study, using an 11-point numerical rating scale (the Brief Pain Inventory) with five pain modalities from 0 (= no pain) to 10 (= worst pain imaginable) - Adverse experiences: Assessed by patient at baseline and daily during titration in addition to the following times: (1) when the patient is clinically stabilised on first line opioid, (2) if the patient does not respond to first-line opioid and requires switching to alternative opioid, (3) when patient is clinically stabilised on second line opioid, (4) if the patient's analgesic requirement have increase by 200% of their initial stable opioid dose, and (5) if the patient does not respond to second line opioid or fits the criteria to exit the study, using an 11-point numerical rating scale from 0 (= no symptom) to 10 (= worst symptom severity imaginable) for nausea, vomiting, constipation, diarrhoea, drowsiness, confusion or disorientation or hallucinations, bad dreams and other notable symptoms.

	During assessments patients were also asked to report any new adverse events - Responding patients (primary outcome): Defined as patients who responded clinically to morphine and oxycodone when used as the first line strong opioid in cancer-related pain, that is, opioid non-response was classified as inadequate analgesia despite dose escalation or intolerable side effects, or both, and adequacy of pain control and tolerability of side effects were defined by patients' subjective assessment, regardless of score
Notes	- Study free of commercial funding? "This study was funded by the Palliative Care Research Fund from the Royal Marsden Hospital, St. Joseph's Hospice, the Asmarley Trust, and an unrestricted educational grant from Napp Pharmaceuticals. None of the funding bodies had any role in the design and conduct of the study, the collection, management, analysis, or interpretation of the data, and the preparation, review, and approval of the manuscript, or in the decision to submit for publication. The authors report no conflicts of interest. The study also was supported by the National Institute for Health Research Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College London. " - Groups comparable at baseline? Yes, the groups seem to be comparable at baseline - ITT analyses undertaken? Yes for efficacy, but data only included for 153/198 patients for safety

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomized to either morphine or oxycodone in a 1:1 ratio via computer-generated random permuted blocks. "
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) Pain	High risk	"This independent study was an open-label one because of safety, logistical, and financial considerations."
Blinding of participants and personnel (performance bias) Adverse events	High risk	See cell above
Blinding of outcome assessment (detection bias) Pain	High risk	Patient-assessed. See cell above
Blinding of outcome assessment (detection bias) Adverse events	High risk	See cell above

Incomplete outcome data (attrition bias) Pain	High risk	Data only available for 80/100 patients in the oxycodone group and 85/100 in the morphine group for the meta-analyses
Incomplete outcome data (attrition bias) Adverse events	High risk	Adverse events reported for 153/198 patients
Selective reporting (reporting bias)	Low risk	All obvious outcomes are reported
Other bias	Low risk	The study does not appear to be subject to high risk of other biases
Were the patients adequately titrated?	Low risk	Yes, the patients appear to be adequately titrated
For cross-over trials: Are data available for both time periods?	Unclear risk	Not applicable

Salzman 1999

Methods	Design: Randomised, double-blind, parallel group trial Year: Not reported Country: USA
Participants	Patients: 50 patients randomised; 48/50 patients received ≥ 1 dose of study medication; N = 24 in each group. 35/50 patients completed the titration period, 3 patients discontinued the study due to adverse events, 8 due to ineffective treatment or intercurrent illnesses, and 2 due to other reasons Controlled-release group: 8 males and 16 females, mean (range) age = 60 (25 to 77) years; patients taking pre-study opioids: Yes: N = 23, No: N = 1 Immediate-release group:13 males and 11 females, mean (range) age = 61 (39 to 91) years; patients taking pre-study opioids: Yes: N = 22, No: N = 2 Inclusion criteria: Patients aged ≥ 18 years with stable cancer pain not adequately controlled by prior analgesic therapy with or without opioids. Among patients who were receiving nonopioid analgesic therapy, the dosing regimen was stabilised ≥ 1 week before the initiation of study medication and remained stable for the duration of the studies Exclusion criteria: "Patients excluded from the studies included individuals with an allergy or contraindication to opioid therapy; patients with a history of substance abuse; patients receiving an opioid analgesic that could not be discontinued; cancer patients prescribed oral oxycodone at a total dose of more than 400 mg/day"
Interventions	Oxycodone arm - Drug: Oxycodone - Dose and dosing: Starting dose for opioid-naive patients = 20 mg/day, and for non-opioid-naive patients the starting dose was based on the prior 3 days of analgesic therapy; every 12 hours at 8 am and 8 pm (± 1 hour each time). Mean final daily dose (SE) = 104 (20) mg - Formulation: Controlled-release

	- Route of administration: Oral - Length of treatment: Up to 21 days - Titration schedule: "The starting dose was titrated upward in each study to a limit of 400 mg/day..... Among those who required titration, the dose was increased until the patients rated their level of pain at an intensity of no greater than "slight" (1.5) on the CAT scale. The dose could be adjusted every 24 to 48 hours if necessary. Criteria for stable pain control were said to be met if pain was stabilized at 1.5 or below for 48 hours while patients were taking no more than two doses per day of supplemental analgesic." - Rescue medication: "Supplemental analgesic was permitted as needed for control of breakthrough or incident pain and was provided in doses of 5 mg IR oxycodone (1 tablet) for patients titrated to 20 to 40 mg/day and 10 mg IR oxycodone (2 X 5 mg tablets) for patients titrated to 60 to 80 mg/day. For patients receiving doses greater than 80 mg/day, the supplemental analgesic dose was approximately 1/6 of the patient's total daily oxycodone dose rounded to the nearest 5 mg. Rescue medication was taken no more than once every 4 hours." - Other medication: "All other opioid analgesics were prohibited. Besides nonopioid analgesic medications (discussed above), other medications necessary for patients' welfare were administered under the supervision of the investigator/physician" Comparison arm - Drug: Oxycodone - Dose and dosing: Starting dose for opioid-naive patients = 20 mg/day, and for non-opioid-naive patients the starting dose was based on the prior 3 days of analgesic therapy; four times daily at 8 am, 2 pm, 8 pm and bedtime (± 1 hour each time). The bedtime dose was to be taken ≥ 3 hours after the 8 pm dose. Mean final daily dose (SE) = 113 (24) mg - Formulation: Immediate-release - Route of administration: Oral - Length of treatment: Up to 21 days - Titration schedule: "The starting dose was titrated upward in each study to a limit of 400 mg/day..... Among those who required titration, the dose was increased until the patients rated their level of pain at an intensity of no greater than "slight" (1.5) on the CAT scale. The dose could be adjusted every 24 to 48 hours if necessary. Criteria for stable pain control were said to be met if pain was stabilized at 1.5 or below for 48 hours while patients were taking no more than two doses per day of supplemental analgesic." - Rescue medication: "Supplemental analgesic was permitted as needed for control of breakthrough or incident pain and was provided in doses of 5 mg IR oxycodone (1 tablet) for patients titrated to 20 to 40 mg/day and 10 mg IR oxycodone (2 X 5 mg tablets) for patients titrated to 60 to 80 mg/day. For patients receiving doses greater than 80 mg/day, the supplemental analgesic dose was approximately 1/6 of the patient's total daily oxycodone dose rounded to the nearest 5 mg. Rescue medication was taken no more than once every 4 hours." - Other medication: "All other opioid analgesics were prohibited. Besides nonopioid analgesic medications (discussed above), other medications necessary for patients' welfare were administered under the supervision of the investigator/physician"
Outcomes	- Pain intensity: Assessed by patient in daily diary, using a categorical scale from 0 (= none) (1 = slight, 2 = moderate) to 3 (= severe). Also assessed at the clinic visit at the end of the titration period - Adverse events: Assessed by patient in daily diary, using a categorical scale from 0 (=

	none) (1 = slight, 2 = moderate) to 3 (= severe). Also assessed at the clinic visit at the end of the titration period - Time to stable pain control was recorded as zero for patients meeting the criteria for success in the first 48 hours (i.e., no titration was needed)."
Notes	- Study free of commercial funding? No. The study was sponsored by the drug manufacturer (Purdue Pharma L.P.) and some of the authors were employees of the study drug manufacturer - Groups comparable at baseline? The groups appear to be comparable at baseline - ITT analyses undertaken? Yes, it seems so for adverse events where the data from 48/50 patients are analysed, but only the data from 35/50 are analysed for pain intensity as only 35/50 patients completed the titration phase

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) Pain	High risk	The study was open-label
Blinding of participants and personnel (performance bias) Adverse events	High risk	The study was open-label
Blinding of outcome assessment (detection bias) Pain	High risk	The study was open-label
Blinding of outcome assessment (detection bias) Adverse events	High risk	The study was open-label
Incomplete outcome data (attrition bias) Pain	High risk	Data reported for 35/50 patients
Incomplete outcome data (attrition bias) Adverse events	Low risk	Data reported for 48/50 patients
Selective reporting (reporting bias)	Low risk	All obvious outcomes appear to be reported
Other bias	Low risk	The study does not appear to be subject to high risk of other biases

Salzman 1999 (*Continued*)

Were the patients adequately titrated?	Unclear risk	Not applicable. This study was a titration study
For cross-over trials: Are data available for both time periods?	Unclear risk	Not applicable

Stambaugh 2001

Methods	Design: Randomised, double-blind, cross-over trial Year: Not reported Country: USA
Participants	Patients: 40 patients entered; 30/40 patients completed both of the double-blind periods with 100% compliance; 9 patients discontinued the study during the titration phase due to adverse events (2), lack of efficacy (4), intercurrent illness (1), and 'other' reasons (2) , and 1 patient discontinued the study during the double-blind phase due to weakness secondary to progressive disease 10 males and 20 females, mean (range) age = 60 (34 to 83) years; primary pain site was bone (27), viscera (1), and other (2). All patients were receiving therapy that included opioids pre-study Inclusion criteria: Patients aged > 18 years with moderate or severe cancer-related pain who did not require > 240 mg/day oral oxycodone equivalent for pain relief who were able to take oral medication and and practiced a medically acceptable method of birth control if female with childbearing potential Exclusion criteria: Primary tumour or metastatic disease in the brain, received chemotherapy within 3 days of study entry, drug abuse, severe cognitive impairment, compromised hepatic or renal function, radiotherapy to the pain site, or hypersensitivity to oxycodone
Interventions	Oxycodone arm - Drug: Oxycodone + placebo - Dose and dosing: The total 24-hour oxycodone dose was equal to the stable daily dose obtained at the end of the titration phase. Drug administration 4 times daily consisting of oxycodone interspersed with placebo, resulting in q12h dosing of oxycodone. Mean final daily dose is not reported - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: Up to 35 days, consisting of a titration period of 2-21 days, followed by two double-blind cross-over periods each lasting 3 to 7 days - Titration schedule: Open-label with immediate-release oxycodone, starting dose was comparable to that calculated, based on the past 3 days of analgesia therapy. "The subjects completed the titration phase at home while monitored on a daily basis by telephone by the research monitor. Recommendations regarding changes in in medication were used to minimize oxycodone use while providing adequate analgesia. More than 2 rescue medication doses per 24-hour period or a moderate or severe global pain score indicated inadequate pain control. Patients whose pain was inadequately controlled after 21 days or who required more than 240 mg or less than 20 of oxycodone daily were discontinued

	from the study" - Rescue medication: Immediate-release oxycodone in 5 mg tablets - Other medication: "Concurrent, stable therapy with acetaminophen, NSAIDs, or analgesic adjuvants and coanalgesics were allowed. Opioids other than the study medication were prohibited. All medically necessary but noninvestigational medications were permitted." Comparison arm - Drug: Oxycodone - Dose and dosing: The total 24-hour oxycodone dose was equal to the stable daily dose obtained at the end of the titration phase. Drug administration 4 times daily, qid dosing of oxycodone. Mean final daily dose is not reported - Formulation: Immediate-release - Route of administration: Oral - Length of treatment: Up to 35 days, consisting of a titration period of 2 to 21 days, followed by two double-blind cross-over periods each lasting 3 to 7 days - Titration schedule: Open-label with immediate-release oxycodone, starting dose was comparable to that calculated, based on the past 3 days of analgesia therapy. "The subjects completed the titration phase at home while monitored on a daily basis by telephone by the research monitor. Recommendations regarding changes in in medication were used to minimize oxycodone use while providing adequate analgesia. More than 2 rescue medication doses per 24-hour period or a moderate or severe global pain score indicated inadequate pain control. Patients whose pain was inadequately controlled after 21 days or who required more than 240 mg or less than 20 of oxycodone daily were discontinued from the study". Stable pain control for 48 hours to 10 days was required before entry into the double-blind phase - Rescue medication: Immediate-release oxycodone in 5 mg tablets - Other medication: "Concurrent, stable therapy with acetaminophen, NSAIDs, or analgesic adjuvants and coanalgesics were allowed. Opioids other than the study medication were prohibited. All medically necessary but noninvestigational medications were permitted." - For cross-over trials, cross-over schedule: "After successful completion of period 1, patients were crossed over into the double-blind period 2 without a washout." The procedures for this period were identical to those in period 1
Outcomes	- Pain intensity or pain relief: Assessed by patient in daily diary, using an 11-point scale from 0 (= no pain or no relief) to 10 (= severe pain or complete relief) - Acceptability of treatment: Assessed by patient in daily diary, using a 5-point scale from 1 (= very poor) (2 = poor, 3 = fair, 4 = good) to 5 (= excellent) - Adverse events: Spontaneuosly reported by patient in daily telephone contact
Notes	- Study free of commercial funding? No. The study was sponsored by the drug manufacturer (Purdue Frederick Company) and one of the authors was employed by the study drug manufacturer - Groups comparable at baseline? No details reported about initial group allocation - ITT analyses undertaken? Yes, although only data from 30/40 patients are analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Stambaugh 2001 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias) Pain	Low risk	"The double-blind periods were blinded by using three tablets identical in appearance: 5 mg IR oxycodone, 10 mg CR oxycodone, and placebo."
Blinding of participants and personnel (performance bias) Adverse events	Low risk	See cell above
Blinding of outcome assessment (detection bias) Pain	Low risk	Patient reported outcome. See also cell above
Blinding of outcome assessment (detection bias) Adverse events	Low risk	See cell above
Incomplete outcome data (attrition bias) Pain	High risk	Data from 30/40 patients analysed
Incomplete outcome data (attrition bias) Adverse events	High risk	See cell above
Selective reporting (reporting bias)	Low risk	All obvious outcomes appear to be reported
Other bias	Low risk	The study does not appear to be subject to high risk of other biases
Were the patients adequately titrated?	Low risk	The patients were probably adequately titrated. Pain intensity dropped from 6 (SD = 2.2) at the beginning of titration to 2.7 at the completion of the titration phase
For cross-over trials: Are data available for both time periods?	Low risk	Yes, data are available for both study periods for 30/40 patients

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmedzai 2012	Comparison not in PICO: Oxycodone-naloxone versus oxycodone
Chen 2009	Comparison not in PICO: Oxycodone-acetominophen versus morphine
Dunlop 2013	Comparison not in PICO: Oxycodone-naloxone versus oxycodone
Garassino 2010	Comparison not in PICO: Fixed-dose oxycodone and increasing dose of pregabalin versus increasing dose of oxycodone and fixed-dose pregabalin
Garassino 2011	Comparison not in PICO: Fixed-dose oxycodone and increasing dose of pregabalin versus increasing dose of oxycodone and fixed-dose pregabalin
Garassino 2013	Comparison not in PICO: Fixed-dose oxycodone and increasing dose of pregabalin versus increasing dose of oxycodone and fixed-dose pregabalin
Leppert 2011	Comparison not in PICO: Oxycodone-naxolone versus oxycodone
Li 2008	Comparison not in PICO: Oxycodone-acetominophen versus oxycodone
Li 2010	Comparison not in PICO: Oxycodone + gabapentin versus oxycodone
Meng 2008	Published completely in Chinese. Translator confirmed that the study is not an RCT, but rather a retrospective review of cancer patient charts
NCT01859715	Population not in PICO: "Patients with pain and/or nausea are enrolled in the Emergency Department (ED). They are given either oxycodone, hydrocodone, or ondansetron at the discretion of the Emergency Department (ED) provider or the triage nurse by triage protocol. Detailed prescription, over the counter, herbal, supplement, and illicit drug ingestion histories are taken from the patient or their health care proxy. Serial visual analogue scales are captured prior to study drug administration then between 30 and 90 minutes following drug administration. " "Subjects given either oxycodone 5mg or hydrocodone/acetaminophen 5mg/500 mg by ED provider decision or by triage nurse randomization." Unclear whether it is a RCT
NCT01885182	Comparison not in PICO: Oxycodone-naxolone versus oxycodone
Pang 2009	Comparison not in PICO: fixed doses of oxycodone-acetominophen versus background doses of oxycodone-acetominophen plus additional dose for breakout pain versus controlled-release oxycodone plus oxycodone-acetominophen for breakout pain
Shi 2008	Comparison not in PICO: Oxycodone-acetominophen versus morphine
Sima 2010	Comparison not in PICO: Oxycodone + aceteminophen versus placebo
Sima 2010a	Comparison not in PICO: Oxycodone + aceteminophen versus placebo

(*Continued*)

Sima 2012	Comparison not in PICO: Oxycodone + paracetamol versus placebo
Stambaugh 1980	Comparison not in PICO: Oxycodone-acetominophen (tylox) versus oxycodone-aspirin (Percodan)
Stambaugh 1980a	Comparison not in PICO: Oxycodone + aspirin + caffiene + phenaticin (Percodan) versus zomepirac versus placebo
Stambaugh 1981	Comparison not in PICO: Oxycodone + aspirin + caffiene + phenaticin (Percodan) versus zomepirac versus placebo
Stambaugh 1987	Comparison not in PICO: Xorphanol versus oxycodone-acetominophen versus placebo
Stambaugh 1990	Comparison not in PICO: Flurbiprofen versus oxycodone-acetominophen versus placebo
Wu 2009	Comparison not in PICO: Oxycodone-acetominophen versus tramadol
Xiong 2008	Comparison not in PICO: Oxycodone-acetominophen versus morphine
Zou 2009	Comparison not in PICO: Oxycodone + acetaminophen versus increased dose of existing opioid treatment

Characteristics of studies awaiting assessment *[ordered by study ID]*

2012-001578-26

Methods	Randomised, parallel-group, open-label controlled trial: An International, Multicentre, Open Randomised Parallel Group Trial Comparing a Two Step Approach for Cancer Pain Relief With the Standard Three Step Approach of the WHO Analgesic Ladder in Patients With Cancer Pain Requiring Step 2 Analgesia
Participants	Inclusion Criteria: - 18 years of age and over. - Patient has a cancer diagnosis (based on radiological, histological, cytological, or operative evidence). Those with haematological malignancies are eligible - Cancer related pain - which in the opinion of the clinician is caused by the presence of tumour or metastases - Average pain score > 4, on a numerical rating scale from 0 to 10, requiring step 2 analgesia (weak opioid) - Patient is able to comply with trial procedures Exclusion criteria: - Patients who have received radiotherapy in the previous 6 weeks or are planned to receive radiotherapy during the trial period where in either case, it is expected to affect pain during the trial period - Pain due to surgery in the preceding 4 weeks - Life expectancy less than two months (based on clinical impression) - Patients with psychotic disorders or cognitive impairment - Patients who have received regular doses (scheduled doses - not as required dosing) of weak or strong opioids in the preceding two weeks - Patients using immediate-release opioids > 2 doses/24 hours, in the previous 24 hours

2012-001578-26 (*Continued*)

Interventions	Standard 3 Step approach (patients will be managed according to the standard 3 Step approach of the WHO analgesic ladder (Step 1 - Step 2 - Step 3)) versus 2 Step approach (patients managed according to the WHO analgesic ladder bypassing Step 2, i.e., patients will move from Step 1 of the WHO analgesic ladder to Step 3) Drugs to be used: Oral morphine, oral oxycodone, oral tramadol, codeine
Outcomes	Primary outcome measures: - Time to achieving stable pain control, where stable pain control is defined as the first day of three consecutive days with average pain score less than or equal to 3 using scores from the Patient Diary and patient assessments. (Time frame: Up to 20 days) Secondary outcome measures: - Mean of daily average pain scores from the Patient Diary - Mean of daily worst pain scores from the Patient Diary - Percentage of days with average pain score $\geq$ 6 from the Patient Diary - Percentage of days with worst pain score $\geq$ 6 from the Patient Diary - Pain intensity, pain relief, and pain interference scores at day 10 and 20 from the Brief Pain Inventory - Patient distress score at day 10 and 20 from the NCCN Distress Thermometer
Notes	Location: UK, Norway, Australia, Italy, Germany, Uganda, Spain Sponsors and collaborators: University of Edinburgh, NHS Lothian, Mundipharma (UK), St Olavs Hospital (Norway) Principal investigators: Marie Fallon, University of Edinburgh Target enrolment: N = 450 Study dates: March 2012 to December 2014 Other study ID numbers: NCT01493635, 11/SS/0079

Aurilio 2009

Methods	Poster Presentations **Session title:** Chronic pain **Presentation date:** Sunday, 15 March 2009 **Evaluation of efficacy and safety of prolonged-release oxycodone at different dosages for the treatment of severe chronic pain** Aurilio C, Sansone P, Pace MC, Passavanti MB, Romano SV, Pota V Second University of Naples, Department of Anaesthesiological, Surgical and Emergency Sciences, Napoli, Italy **Background and aims:** It's important to arrange a correct and flexible therapy for the treatment of chronic malignant and non-malignant pain especially in fragile patients. The aim of this study is to evaluate the efficacy and safety of prolonged-release (PR) oxycodone 10 mg/morning and 20 mg/evening versus PR oxycodone 20 mg twice a day **Methods:** After local ethical committee approval and written informed consent 40 patients (13 men and 27 women) , affected by severe chronic pain (mean NRS 8) were randomised in two groups: OD group: 20 patients receiving PR oxycodone 10 /morning and 20 /evening; OS Group: 20 patients who receiving PR oxycodone 20 mg every 12 hours. The observation period was 28 days with 5 visits, once a week (T0 to T5). NRS was the parameter of efficacy while the incidence and intensity of nausea, vomiting, somnolence, stipsis and itching were the parameters of safety. Any assumption of rescue medication (immediate-release oral morphine 10 mg) was registered **Results:** Both the groups presented a 50% reduction of pain T1, and kept a very good analgesia for all the observation period. In OD group there was a lower incidence of adverse events than in OS Group. In OS group there was a lower assumption of rescue medication than in OD Group **Conclusion:** Therapy using PR oxycodone at different dosages allows a pain reduction similar to therapy with PR oxycodone at same dosage. Moreover with this therapeutic scheme it's possible to reduce the incidence of adverse events
Participants	E-mailed authors to ask for clarification re population on 23 May 2013
Interventions	
Outcomes	
Notes	

JapicCTI-090789/090/091

Methods	JapicCTI-090789: An open-label study of intravenous (i.v.) S-811717 (oxycodone hydrochloride solution for injection) in patients with cancer pain JapicCTI-090790: An extension study of S-811717 (oxycodone hydrochloride solution for injection) in patients with cancer pain JapicCTI-090791: An open-label study of subcutaneous injection (s.c.) S-811717 (oxycodone hydrochloride solution for injection) in patients with cancer pain
Participants	Inpatients with pain associated with various cancers aged $\geq$ 20 years
Interventions	S-811717
Outcomes	- To evaluate the efficacy and safety of S-811717 in patients with pain caused by various cancers - To determine the pharmacokinetics of S-811717 and its metabolites. No other information available

JapicCTI-090789/090/091 (*Continued*)

Notes	Location: Japan Sponsors, collaborators, investigators: Shionogi & Co, Ltd., Research and Development No other information available

NCT00378937

Methods	An Open, Randomized, Parallel Group Study in Patients With Cancer Pain, To Compare a Two-Step Analgesic Ladder (Non-Opioid to Oxycodone) With Conventional Management Using A Three-Step Approach
Participants	Disease characteristics: - Diagnosis of cancer - Requires regular step-2 analgesia for the management of cancer-related pain Patient characteristics: - Aged ≥ 18 years - Not pregnant or nursing - Fertile patients must use effective contraception - Must be able to take oral medicationMust be willing and able to complete a daily patient assessment booklet (PAB) - No history of the following conditions: Depression, personality disorders that may lead to self-harm, admission to the hospital for psychiatric reasons, any other psychological disorder that, in the opinion of the investigator, would preclude study treatment - Not at risk of additional CNS depressant effects due to study drugs - No known history of alcohol or drug abuse or, in the opinion of the investigator, tendency towards drug abuse or addiction - No current abuse of alcohol or drugs - No known sensitivity to oxycodone hydrochloride or other opioids - No history of a specific or allergic reaction to study drugs - No contraindications as a result of adverse drug reaction or drug interactions of oxycodone or other opioid drugs - No other condition that, in the opinion of the investigator, would make the patient unsuitable for study participation Prior concurrent therapy: - More than 30 days since prior and no concurrent chemotherapy or radiotherapy - At least 2 weeks since prior regular (i.e., 4 times per day) step-2 analgesics - More than 3 months since prior regular use of opioids, defined as having a regular prescription of an opioid medication - Not planning to undergo cancer-related surgery - No other concurrent opioid-based medication other than oxycodone hydrochloride capsules as escape medication (arm II) - No concurrent participation in another clinical trial involving a new chemical entity
Interventions	Arm 1: Patients receive an analgesic regimen, according to their level of pain, for up to 18 weeks - Step 1: Patients in mild pain receive oral acetaminophen 4 times daily - Step 2: Patients in mild-to-moderate pain receive oral codeine or oral dextropropoxyphene hydrochloride 4 times daily and oral acetaminophen 4 times daily - Step 3: Patients in moderate-to-severe pain receive oral morphine or oral oxycodone hydrochloride 6 times daily (every 4 hours) with or without a non-opioid analgesic Patients may also receive an adjuvant drug (i.e., for side effects or for primary indication other than pain management that is analgesic in selected circumstances) versus Arm 2: Patients receive oral oxycodone hydrochloride twice daily for up to 18 weeks. Patients may receive a different

NCT00378937 (*Continued*)

	opioid analgesic or analgesia or adjuvant medication as in arm I, if needed Patients in both arms may also receive additional medication for breakthrough pain. Patients complete a patient-assessment booklet (PAB) daily which includes a Box-Scale (BS)-11 rating for average pain; questions regarding contact (e.g., telephone or visit) with healthcare professionals on that day; and information regarding the number of times escape medication is used. Quality of life and levels of cancer pain are assessed using the short form of the Brief Pain Inventory (BPI). After completion of study treatment, patients are followed at 4 weeks
Outcomes	Primary Outcome Measures: - Percentage of time in assessment periods 1 and 2 (i.e., first 4 weeks) with a BS-11 pain score of ≤ 4 (i.e., mild pain) Secondary Outcome Measures: - Percentage of time in assessment periods 3 and 4 with a BS-11 pain score of ≤ 4 - Mean BS-11 pain scores - Time to reach stable pain control - Mean escape medication use - Quality of sleep - Global assessment of pain relief with study drugs - Mean pain intensity, pain interference, and pain relief scores as measured by the BPI - Overall number of phone calls, home visits by a nurse, home visits by a doctor, and unscheduled visits to a healthcare provider, related to pain control or analgesic medication during study treatment
Notes	Location: US Sponsors and collaborators: University Hospitals Bristol NHS Trust Study chair: Geoff Hanks, University Hospitals Bristol NHS Trust Target enrolment: N = 30 Study dates: ? Other study ID numbers: CDR0000507650, CRUK-ON/2003/1772, EU-20640, EUDRACT-2004-004235-66, NAPP-CRUK-ON/2003/1772

NCT00726830

Methods	Randomised, parallel-group, open-label controlled trial: A Randomized Comparison of Oral Methadone as a "First-Switch" Opioid Versus Opioid Switching Between Sustained-Release Morphine and Oxycodone for Oncology-Hematology Outpatients With Pain Management Problems: The "Simply Rotate" Study
Participants	Disease characteristics: - Receiving ongoing care in the outpatient medical oncology setting - Self-reported pain (of any cause) for which long-acting strong opioids (morphine or oxycodone) have been prescribed or administered oral morphine-equivalent daily dose (MEDD) of existing opioid regimen (long-acting or immediate-release) 40 to 300 mg/day - Worst pain score on a scale of 0 (no pain) to 10 (worst pain) of ≥ 5 for ≥ 1 week duration based on verbal self-report or ≥ 1 persistently bothersome symptom attributed to an opioid side effect (e.g., fatigue, confusion, depressed level of consciousness, memory loss, personality change, anorexia, constipation, dehydration, nausea, vomiting, weight loss, pruritus, urticaria, impotence, reduced libido, and urinary retention or hesitancy), or both Patient characteristics: - Aged ≥ 18 years - None of the following conditions that could predispose the patient to prolonged QT interval-associated tachycardia: serum potassium < 3.0 mg/dL; cocaine abuse within the past 3 months; family history of sudden death; advanced heart failure (ejection fraction < 40% or New York Heart Association (NYHA) class III or IV heart disease, or both

	- No known or suspected cognitive impairment that could interfere with adherence to the medication plan or self-report of symptoms and side effects - Not pregnant or nursing - Fertile patients must use effective contraception Prior concurrent therapy: - See 'Disease characteristics' - More than 4 weeks since prior radiotherapy or surgery for local control of cancer or pain palliation - More than 60 days since prior use of the same long-acting opioid (i.e., the new long-acting opioid) that patient is switching to on the study - More than 12 weeks since prior methadone therapy - More than 3 days since prior and no concurrent transdermal fentanyl, oxymorphone, or buprenorphine - Concurrent systemic anticancer therapy or bisphosphonates allowed provided therapy was initiated ≥ 4 weeks ago - Concurrent tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, or other adjuvant analgesics or psychostimulants allowed provided therapy was initiated ≥ 2 weeks ago; dose expected to remain stable until after the first week of opioid rotation on study - No concurrent methadone maintenance therapy for opioid addiction - No concurrent intrathecal infusion of analgesics - No concurrent antiarrhythmic medications (e.g., amiodarone or quinidine)
Interventions	Opioid rotation to oral methadone (participants are switched from their current opioid medication (oxycodone or morphine) to methadone. Participants receive oral methadone 2 to 3 times daily for 4 weeks) versus Opioid rotation to another long-acting strong opioid (participants currently receiving oxycodone are switched to sustained-release (SR) morphine. Participants currently receiving morphine are switched to SR oxycodone. Participants receive either oral SR morphine or oxycodone 2 to 3 times daily for 4 weeks)
Outcomes	Primary outcome measures: - Number of participants with at least a 3-point reduction in pain score on the M.D. Anderson Symptom Inventory (MDASI) (time frame: 28 days) - MDASI questionnaire completed on days 8, 15, and 22 after enrollment. The 'primary success' is defined as a 3-point reduction in pain score on the MDASI. Scores from baseline and from four weeks later compared using the MDASI average pain intensity on a scale of 0 (no pain) to 10 (worst pain) Secondary outcome measures: - Number of participants with 30% reduction in total summary score for the Individual Composite Drug Toxicity Score (CDTS) Items (time frame: 28 days) (Designated as safety issue)
Notes	Location: US Sponsors and collaborators: M.D. Anderson Cancer Institute, National Cancer Institute Principal investigators: Michael J Fisch, MD, Anderson Cancer Center; James D Bearden, CCOP - Upstate Carolina Target enrolment: N = ? Study dates: March 2009 to October 2010 Other study ID numbers: 2007-0791, MDA-2007-0791, CDR0000598283

Song 2009

Methods	It is unclear whether this is a retrospective study or a randomised controlled trial. Authors e-mailed on 14 January 2014 for clarification Design: 'Randomized', parallel-group Year: 2006 to 2008 Country: China
Participants	Patients: - Oxycodone (commercial name Tai Lening): N = 42, 42 analysed, M/F = unclear, median (range) age = 55 (28 to 83) years. Primary tumours were: lung cancer (12) , breast cancer (5), liver cancer (6), gastric cancer (4), nasopharyngeal carcinoma (3), colorectal cancer (3), oesophageal cancer (3), lymphoma (2), osteosarcoma (2), chordoma (1) , pancreatic cancer (1) - Morphine sulfate controlled-release (MS Contin): N = 45, 45 analysed, 27 males and 18 females; median (range) age = 53 (30 to 76) years. Primary tumours were: Lung cancer (14), breast cancer (6), liver cancer (6); gastric cancer (6), oesophageal cancer (3), pancreatic cancer (2), nasopharyngeal (2), colorectal cancer (2), non-Hodgkin's lymphoma (2), ovarian cancer (2) Inclusion criteria: "87 patients who were diagnosed with malignant tumour based on histopathology and cytology, with moderate to severe cancer pain and who did not respond to non-steroidal anti-inflammatory drugs and weak opioid analgesics" Exclusion criteria: Not reported
Interventions	Oxycodone arm - Drug: Oxycodone + 1 tablet (each containing oxycodone 5 mg, acetaminophen 325 mg), - Dose and dosing: every 6 h (2 oxycodone tables has equal titration dose with oral morphine 30 to 40 mg) - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 5 days - Titration schedule: Not clear but seems they have same dose increased as the contin group - Rescue medication: During the treatment, if patients have short term unsatisfactory treatment efficacy or have sudden intensified pain, then short-acting morphine injection was administrated. The patients were considered treatment failure if the pain relief was not relieved until the observation period had ended or the limit dose was reached - Other medication: Unclear Comparison arm - Drug: Morphine sulfate (MS Contin) - Dose and dosing: 20 mg/day as the first dose - Formulation: Controlled-release - Route of administration: Oral - Length of treatment: 5 days - Titration schedule: MS Contin group with 20 mg/day as the first dose, if the pain could be relieved, then continued using the same dose as maintenance treatment. If the pain was not relieved after 24 hr, then increased the dose until a satisfactory pain relief, or till reach the maximum dose (the maximum dose = 270 mg/day) - Rescue medication: During the treatment, if patients have short-term unsatisfactory treatment efficacy or have sudden intensified pain, then short-acting morphine injection was administrated. The patients were considered treatment failure if the pain relief was not relieved until the observation period had ended or the limit dose was reached - Other medication: Unclear For both groups, if the patients had intolerable adverse reactions when increasing the dose, the drugs could be discontinued at any time, then the patients were observed 30 days and then evaluated the treatment efficacy The patient was also considered as treatment failure if the treatment has to be stopped due to intolerable adverse events

Outcomes	- Pain Intensity (PI) and pain relief: the WHO linear Visual Analog Scale VAS was used, the degree of pain was graded using by dividing a line into 10 segments: 0 = no pain, 1 to 3 as mild, 4 to 7 as moderate, severe pain as 8 to 9, 10 = extreme pain Complete remission (CR): completely no pain after treatment, with a pain score of 0 on a 0 to 10 VAS. Partial remission (PR): pain reduced significantly, there was no sleep disturbance, have normal daily life, the pain reduced 4 or more grades in the segments.(YY's note: they did not say scores lower than 4, they said reduced 4 or more, CR can be translated as complete relief). Mild remission (NC): certain degree of pain relief, but require enhanced pain control, patients had sleep disturbances, VAS score reduced 1 to 3 grades in the 0 to 10 VAS line. (YY note, NC normally means no changes). Treatment failure (PD): no pain relief compared to baseline. (YY note - PD normally means progression of disease). The authors considered patients who were CR or PR as "treatment was effective" - Adverse reactions. Patients were observed for all kinds of adverse reactions: constipation, nausea, vomiting, dizziness, drowsiness, skin rash or itching, abdominal discomfort etc
Notes	Study free of commercial funding? Unclear Were the patients adequately titrated? Unclear, possibly? Groups comparable at baseline? Unclear, probably if properly randomised ITT analyses undertaken? Yes

Characteristics of ongoing studies *[ordered by study ID]*

2006-003151-21

Trial name or title	Study to compare the tolerability of slow release oxycodone versus slow release morphine in the treatment of severe cancer pain. The study is geared towards a clinical practice improvement
Methods	Randomised, parallel-group, open controlled trial
Participants	Inclusion criteria: - Patients older than 18 years of age - Patients with oncological referred pain within the 24 hours preceding the initial administration of treatment with an intensity of greater than or equal to 5 measured by the numerical scale NRS of 11 levels 0 to 10 - Patients who did not take other analgesics or who only took NSAIDs and/or weak opioids either I or II on the WHO scale - Patients have given their written consent - Patients in the study have been given at least one month to live - Patients are required to follow the treatment regiment for at least 2 weeks under clinical observation - Patients with KPS greater than or equal to 40 Exclusion criteria: - Treatment with morphine, oxycodone, buprenorphine, fentanyl, or methadone in the 30 days leading up to the study - Patients whose medical history, based on the opinions of a physicians, is significant for intolerance to morphine or oxycodone - Patients whose doctors have suggested they should add ex novo another analgesic adjuvant steroids, anti-convulsants, antidepressants - Patients with severe renal impairment - Patients with moderate to severe hepatic insufficiency. Patients with dyspnea or severe BPCO - Patients who are not able to be treated taking oral medications as recommended by the WHO guidelines

2006-003151-21 (*Continued*)

	- Patients who have a history of ongoing psychiatric illness - Patients with cognitive deficit that cannot consent to the treatment and will not comply with the treatment protocol - Patients with cerebral metastasis - Patients who are either pregnant or breast feeding
Interventions	Oxycodone (prolonged-release oral tablet) versus morphine (slow-release)
Outcomes	The primary outcome variable is the dichotomous variable that indicates a worsening, in the first 14 days of treatment, of at least one of the following adverse effects nausea, vomiting, hallucinations, mental confusion, constipation, sedation, dry mouth, itching. The patient was defined to have deteriorated if, in respect to the baseline evaluation, he registered a worsening of at least 2 points of a scale of 0 to 10 for at least one of the symptoms considered and for at least one of the two weeks of treatment. For hallucinations the worsening is indicated by the presence of at least one episode during the two weeks of treatment
Starting date	Not reported
Contact information	Location: Italy Sponsors: Istituto Nazionale Per La Cura Tumori Principal investigators: Not reported
Notes	Target enrolment: N = 400 Study completion date: ? but of 1-year duration Other study ID numbers: None reported

2008-002273-12

Trial name or title	Long term opioid administration in oncologic chronic pain: open label, prospective study on efficacy, safety and pharmacogenetic factors
Methods	Randomised, parallel-group, open controlled trial
Participants	Inclusion criteria: - age > 18 years - oncologic, chronic, neurophatic or nociceptive peripheral pain Exclusion criteria: - abuse history - opioid analgesic use history - opioid allergies
Interventions	Morphine (oral solution) versus morphine (oral tablet) versus oxycodone (oral tablet) versus

2008-002273-12 (*Continued*)

	fentanyl (transdermal patch) versus buprenorphine (transdermal patch) versus hydromorphone (prolonged-release oral tablet)
Outcomes	Pain reduction at least 40% in VAS scale
Starting date	Not reported
Contact information	Location: Italy Sponsors: Ospedale Policlinico S. Matteo Principal investigators: Not reported
Notes	Target enrolment: N = 320 Study completion date: ? but of 3-year duration Other study ID numbers: None reported, but is it the same as NCT00916890 below?

2009-013118-28

Trial name or title	Bukkaalinen fentanyyli syöpäpotilaiden toimenpidekivun hoidossa ("The buccal fentanyl in cancer pain management measure")
Methods	Randomised, cross-over (open or blind?) controlled trial
Participants	Inclusion criteria: - Cancer metastatic to the bone - beginning radiotherapy to bone metastases (?) Exclusion criteria: - Severe hepatic, renal or cardiac dysfunction - uncontrolled or rapidly increasing pain - dry mouth - oral mucositis or stomatitis - pregnancy or breastfeeding - impaired cognitive performance - increased intracranial pressure - drug abuse or history of drug use within the previous 5 years, or of use of CYP3A4 inhibition drug(s?) (translated from Finnish)
Interventions	Fentanyl (buccal) versus oxycodone (oral) (Oxynorm)
Outcomes	Pain relief and speed of effect for fentanyl compared to oxycodone, radiation therapy-related acute, short-term pain relief (translated from Finnish), side effects
Starting date	Not reported

2009-013118-28 (*Continued*)

Contact information	Location: Finland Sponsors: Tarja Heiskanen Principal investigators: Not reported
Notes	Target enrolment: N = ? Study completion date: ? Other study ID numbers: None reported

2010-020402-15

Trial name or title	Randomised, double-blind, cross-over Phase III study to investigate the efficacy and safety of oxycodone after once daily administration of oxycodone HCl XL tablets in comparison to twice daily administration of Oxygesic® tablets in patients with chronic pain
Methods	Randomised, double-blind, cross-over controlled trial
Participants	Inclusion criteria: - Caucasian male and female patients ≥18 years of age with chronic cancer pain - Patients with predominantly non-neuropathic pain - Patients requiring continuous oral opioid therapy with at least 40 mg oxycodone per day (or equivalent) - Adequate analgesia (mean 'current' pain intensity per day ≤ 40 mm on VAS) prior to randomisation for at least three consecutive days - Stable analgesic requirements prior to randomisation for at least three days (stable maintenance dose of oxycodone; requirement of at least 40 mg oxycodone per day; ≤ 2 doses of rescue medication per day), tolerable AEs - ECOG (Eastern Cooperative Oncology Group) performance status < 3 - Life expectancy of at least 3 months - Female patients of childbearing potential agree to undergo pregnancy tests - Willingness to undergo a pre-study physical examination and pre- and post-study laboratory investigations - Ability to comprehend and willingness to sign informed consent Exclusion criteria: - Hypersensitivity to oxycodone or any of the excipients of the study drugs - Patients requiring more than 120 mg oxycodone per day (or equivalent) - Surgery within 1 month prior to study start and/or anticipated or scheduled surgical intervention during the study - Intravenous chemotherapy or radiotherapy, or both, for pain alleviation or neural blockade within 2 weeks prior to study start or anticipated or scheduled during the course of the study, or combinations - Known or suspected clinically significant respiratory depression, hypoxia, hypercapnia, or decrease in respiratory reserve - Known or suspected severe obstructive pulmonary disease, acute or severe bronchial asthma, or cor pulmonale - Known or suspected significant hepatic impairment (hepatic transaminases > 3 times the upper limit of normal) - Known or suspected severe renal impairment (CRCL <30 ml/min) or patients with renal failure who are on any form of dialysis - Known or suspected significant circulatory disturbance, hypotension, or circulatory shock - Known or suspected clinically relevant endocrine disorder, such as myxoedema, not adequately treated hypothyroidism or adrenocortical insufficiency (e.g. Addison's disease)

2010-020402-15 (*Continued*)

	- Known or suspected paralytic ileus, significant impairment of bowel motility severe enough to potentially result in ileus - Known or suspected acute or chronic pancreatitis or biliary tract disease - Any gastro-intestinal pathology or surgery or intractable vomiting likely to significantly influence drug absorption - Inability to swallow the study drugs whole (e.g., due to dysphagia) - Known or suspected significant prostatic hypertrophy or urethral stricture severe enough to potentially result in urinary retention - Known or suspected CNS depression (signs and symptoms: decreased vital signs, impaired thinking and perception, slurred speech, slowed reflexes, fatigue, decreased consciousness), coma, or convulsive disorder - Known or suspected elevation of intracranial pressure - Known or suspected acute alcoholism, delirium tremens, or toxic psychosis - History of drug addiction or drug seeking behaviour - Concomitant treatment with MAO inhibitors - Pregnancy or breast-feeding. Women of childbearing potential unable or unwilling to practice adequate contraceptive measures. Reliable methods for women are orally administered hormonal contraceptives, surgical intervention (e.g., tubal ligation), intrauterine device (IUD) and sexual abstinence - Any other condition of the patient that in the opinion of the investigator may compromise evaluation of the study treatment or may jeopardize patient's compliance or adherence to protocol requirements - Previous enrolment in this study or participation in any other drug investigational trial within the past 30 days (or five half-lives whichever is longer) prior to enrolment - Persons suspected to be at risk of suicide - Persons who are not suitable for inclusion in the study in the opinion of the investigator. Adults, elderly, with chronic cancer pain
Interventions	Oxycodone (once daily administration of oxycodone HCl XL tablets) versus oxycodone (twice daily administration of Oxygesic® tablets)
Outcomes	Primary outcome measures: - Overall 'current' pain intensity (PI) on 0 to 100 mm VAS (mean 'current' PI of the last 5 days of each treatment period). Pain intensity (PI) will be assessed five times daily, i.e., at 08:00 h, 11:00 h, 14:00 h, 17:00 h, and 20:00 h (allowed deviation ± 20 min) on a 0 to 100 mm VAS ('current' pain). PI assessment at 08:00 h and 20:00 h will also comprise ratings of PI over the past 12 hours ('recalled' pain during day- and night-time). From the PI scores the mean 'current' PI over all time points of the last 5 treatment days of period 1 and period 2 (= overall mean 'current' PI) will be calculated for each patient as the primary efficacy endpoint Secondary outcome measures: - mean 'current' pain intensity (PI) per day - mean 'current' PI per time point - mean 'recalled' PI over the past 12 hours at 08:00 h - mean 'recalled' PI over the past 12 hours at 20:00 h - overall effectiveness on 4-point CAT by patient and investigator (assessed at the end of each treatment period) - daily dose of rescue medication for each of the last 5 days of period 1 and 2 - mean daily dose of rescue medication over the last 5 treatment days of period 1 and 2 - total amount of rescue medication over the last 5 treatment days of period 1 and 2
Starting date	3 September 2010

2010-020402-15 (*Continued*)

Contact information	Location: Germany, Hungary (?) Sponsors: Dr Martina Maritz, Develco Pharma Schweiz AG, Hauptstrasse 61, Binningen, 4102 Switzerland: E-mail: m.maritz@develco.ch, tel: +41 614255020, fax: +41 614255029 Principal investigators: Not reported
Notes	Target enrolment: N = 126 Study completion date: 7 February 2012 Other study ID numbers: None reported

Elsayem 2010

Trial name or title	Abstract (this is all the information in the record) TPS324 Background: Methadone is an opioid with many unique pharmacologic properties and it is much less expensive than other opioids commonly used in cancer pain management. It is a particularly attractive analgesic to use for opioid switching, with the goal of improving analgesia and/or decreasing opioid-related side effects. Prospective trials involving methadone for opioid switching are uncommon in publicly-funded, clinical cooperative groups. This trial in progress will help determine the feasibility, safety, and efficacy of two approaches to opioid switching. It will also provide useful information regarding the feasibility of opioid-related research conducted by oncologists in the outpatient community setting Methods: This NCI-funded, randomized, prospective, open-label trial intends to enroll 300 cancer patients in the outpatient community setting. Eligible patients have inadequate pain control and/or intolerable opioid-related side effects and are prescribed either sustained-release morphine or oxycodone, with an oral morphine equivalent daily dose between 40mg and 300mg. Patients are randomly assigned to be rotated to either oral methadone or oral sustained-release morphine or oxycodone, and the new opioid dose is determined using study-specific equianalgesic tables. Patients receive immediate-release opioids for breakthrough pain and supportive measures for side effects, and patients have their opioids titrated according to study protocol Evaluation occurs at enrollment and then weekly for a total of 4 weeks using validated tools that include: M. D. Anderson Symptom Inventory (MDASI), Composite Drug Toxicity Score (CDTS), and Revised Edmonton Staging System (rESS) for Cancer Pain. We hypothesize that 60% of patients rotated to methadone will achieve a 30% reduction in pain and/or opioid-related side effects; whereas 40% of patients rotated to either sustained-release morphine or oxycodone will achieve this response. We define primary success as a 3-point reduction in pain score-measured by MDASI-from baseline to completion of the study No significant financial relationships to disclose
Methods	
Participants	
Interventions	
Outcomes	
Starting date	2010?
Contact information	
Notes	

JapicCTI-132338

Trial name or title	DS-7113b phase III study A randomized double-blind comparison study with immediate release (IR) oxycodone in opioid-naive patients with cancer pain
Methods	A multicentre, active controlled, randomised, double-blind, parallel-group study
Participants	Inclusion criteria: - Both genders, aged ≥ 20 years - Patients receiving non-opioid analgesics for cancer pain, who have not been receiving opioid analgesics - Patients whose VAS is ≥ 35 mm and judged necessary to be treated with strong opioid analgesics - Patients with an ECOG Performance Status (PS) ≤ 3, etc Exclusion criteria: - Patients with symptom(s) or finding(s) falling under the contraindications or relative contraindications stated in the package insert for oxycodone hydrochloride powder and morphine hydrochloride preparations, etc
Interventions	DS-7113b: Each patient will be administered 4 doses a day orally for 5 days, versus Oxycodone hydrochloride powder: Each patient will be administered 4 doses a day orally for 5 days
Outcomes	Primary outcome measures: Change of VAS between pre-treatment and end of treatment Secondary outcome measures: Response rate at end of treatment (analgesia improvement rate), efficacy and safety
Starting date	1 October 2013
Contact information	Location: Japan Sponsors, collaborators, investigators: Daiichi Sankyo Company, Limited Principal investigator: Not reported
Notes	Target enrolment: Not reported Study completion date: 31 March 2015 Other study ID numbers: None reported

NCT00916890

Trial name or title	Chronic Administration of Opioids in Cancer Chronic Pain:an Open Prospective Study on Efficacy, Safety and Pharmacogenetic Factors Influence
Methods	Randomised (parallel group), single-blind (outcome assessor) controlled trial
Participants	Inclusion criteria: - Adult oncologic patients (≥ 18 years old) - Chronic peripheral neuropathic or nociceptive pain, or both - Written informed consent Exclusion criteria: - Pediatric patients

	- Mental impaired patients - Substance abuse disorder - Opioid allergy - History of opioids use or addiction - Severe immunodeficiency, severe renal impairment, severe liver disease - Cachectic state - HIV positive patients
Interventions	Morphine (after a titration phase with fast-release oral morphine, once the optimal dosage (no side effects and less than two rescue doses per day) is reached, an equipotent dose of oral sustained-release morphine will be randomly assigned to a patient) versus oxycodone (after a titration phase with fast-release oral morphine, once the optimal dosage (no side effects and less than two rescue doses per day) is reached, an equipotent dose of oral extended-release oxycodone will be randomly assigned to a patient) versus fentanyl (after a titration phase with fast-release oral morphine, once the optimal dosage (no side effects and less than two rescue doses per day) is reached, an equipotent dosage of transdermal fentanyl will be randomly assigned to a patient) versus buprenorphine (after a titration phase with fast-release oral morphine, once the optimal dosage (no side effects and less than two rescue doses per day) is reached, an equipotent dosage of transdermal buprenorphine will be randomly assigned to a patient)
Outcomes	Primary outcome measures: - To identify the drug with the best clinical-pharmacological safety-efficacy profile among the four opioids: oral extended-release morphine, oral extended-release oxycodone, transdermal fentanyl and transdermal buprenorphine. (Time frame: 15 days after randomisation (Reduction of at least 40% of median daily pain, on a NRS)) "We will define a treatment effective if it will produce a mean reduction of NRS values at least of 40% than basal values. Among all effective treatments, we will identify the best as the one that will have a reduction of NRS to a value of 4 or less in 90% of patients compared to the 70% of the others treatments. To evaluate pharmacological safety the plasma concentrations of the drugs and their metabolites will be measured. We will branch patients population in 3 groups to evaluate the correlation between clinical-pharmacological response and genetics (responder,partially and not responder)." Secondary outcome measures: - Pharmacokinetic of opioids and of their metabolites during long-term administration; correlation between specific genotypes and clinical response or the clinical/pharmacological susceptibility to side-effects on administration of a specific opioid. (Time frame: 6 months (each patient will be followed for 6 month after enrolment with clinical and pharmacological evaluations once a month and if inefficacy, tolerance or side effects)) - Comparison of plasma levels of opioids and of their metabolites in 'responder' patients (clinical effectiveness without side effects), 'partial responder' patients (clinical effectiveness without side effects but taking not more than 2 rescue doses per day), and in 'non-responder' patients (3 groups: clinical inefficacy, side effects, tolerance or opioid induced hyperalgesia). Evaluation of the correlation between the polymorphisms studied and clinical response; the frequency of allelic variants of interest will be compared in 'responder', 'partial responder' and 'non-responder'
Starting date	February 2009

NCT00916890 (*Continued*)

Contact information	Location: Italy Sponsors, collaborators, investigators: IRCCS Policlinico S. Matteo, University of Pavia, Italy Principal investigator: Massimo Allegri, IRCCS Foundation Policlinico "San Matteo", Pavia, Italy; e-mail: m.allegri@smatteo.pv.it, Tel: 00390382502627
Notes	Target enrolment: N = 320 Study completion date: December 2015 Other study ID numbers: PT-SM-1-Op-Cancer

NCT01165281

Trial name or title	A Randomized, Double-Blind, Active Controlled, Optimal Dose Titration, Multicenter Study to Evaluate the Safety and Efficacy of Oral JNS024 Extended Release (ER) in Japanese and Korean Subjects With Moderate to Severe Chronic Malignant Tumor Related Cancer Pain
Methods	Randomised (parallel-group), double-blind (patient, caregiver, investigator) controlled trial
Participants	Inclusion criteria: - Aged ≥ 20 years - Documented clinical diagnosis of any type of cancer - Diagnosis of chronic malignant tumour-related cancer pain with an average score for pain intensity in the past 24 hours of ≥ 4 on the 11-point numerical rating scale (NRS) on the day of randomisation (Day -1) - Have not received treatment with opioid analgesics within 28 days before screening (note: codeine phosphate (≤ 60 mg/d) or dihydrocodeine phosphate (≤ 30 mg/d) for antitussive use are allowed) - Dissatisfied with pain relief by the current treatment and for whom the investigator or designee judges that treatment with opioid analgesics is required Exclusion criteria: - Have complicated with uncontrolled or clinically significant arrhythmia - Have previous or concurrent presence of any disease which may develop increased intracranial pressure, disturbance of consciousness, lethargy, or respiratory problems such as traumatic encephalopathy with cerebral contusion, intracranial hematoma, disturbance of consciousness, brain tumour, cerebral infarction, transient ischemic attack, epilepsy or convulsive diseases - Have history of alcohol or drug abuse - Have any disease for which opioids are contraindicated such as serious respiratory depression of serious chronic obstructive pulmonary disease, bronchial asthma attack, cardiac failure secondary to chronic pulmonary disease, paralytic ileus, status epileptics, tetanus, strychnine poisoning, acute alcohol poisoning, hypersensitivity to opium alkaloid, haemorrhagic colitis, or bacterial diarrhoea
Interventions	R331333 ((referred to as JNS024 ER or CG5503) one 25 mg to 200 mg capsule twice daily for 4 weeks) versus Oxycodone CR (one 5 mg to 40 mg capsule twice daily for 4 weeks)
Outcomes	Primary outcome measures: - The average pain intensity score using an 11-point numerical rating scale (NRS) (time frame: change from baseline to the last 3 days of study drug administration) Secondary outcome measures: - The Patient Global Impression of Change (PGIC) (time frame: at the end of the 4-week double-blind treatment phase)

NCT01165281 (*Continued*)

	- The duration of rescue medication (time frame: during the 4-week double-blind treatment phase) - The concentration of JNS024 in blood samples from patients (time frame: protocol-specified time points during Weeks 1, 2, and 4) - The proportion of patients responding to treatment, including at least 30% and 50%, based on the per cent change from baseline using an 11-point numerical rating score (NRS) (time frame: at Week 4 of the double-blind treatment phase on an 11-point NRS) - Adverse events and findings from clinical laboratory tests, physical examinations, vital signs measurements, and ECG measurements reported (time frame: from time of screening (Days -7 to -1) to post-treatment (Week 5) or time of early termination from study)
Starting date	August 2012
Contact information	Location: Japan, Republic of Korea Sponsors, collaborators, investigators, study director: Janssen Research & Development, L.L.C. Clinical Trial (no other contact information reported)
Notes	Target enrolment: N = 343 Study completion date: August 2012 Other study ID numbers: CR017188, JNS024ER-KAJ-C02

NCT01205126

Trial name or title	A Randomized, Double-Blind, Active Controlled, Multi-center Study to Investigate the Safety and Efficacy of OROS Hydromorphone HCl Once-daily Compared With Oxycodone HCL Controlled-release Twice Daily in Subjects With Cancer Pain
Methods	Randomised (parallel group), double-blind (patient, caregiver, investigator) controlled trial
Participants	Inclusion criteria: - Aged 18 to 70 years - Currently receiving strong oral or transdermal (through the skin) opioid analgesics with inadequate control of moderate to severe cancer pain or currently receiving weak opioids for cancer pain and are eligible according to the study protocol to receive treatment with a strong opioid analgesic - Require or are expected to require between 40 mg and 184 mg of oral morphine or morphine equivalents every 24 hours - Are not expected to start a course of chemotherapy, radiotherapy, target cancer therapy, hormone therapy or diphosphate 2 weeks prior to randomisation or during the study - If receiving long-term treatment including hormone, target cancer therapy and diphosphate, the treatment should keep stable as much as possible from 2 weeks before randomisation and up to the completion of the study - Have a life expectancy of 12 weeks or longer Exclusion criteria: - Have pure neuropathic pain, pain of unknown origin, or acute pain - Have only pain on movement - Are receiving or have received treatment with medical isotopes within the previous 2 weeks prior to randomisation - Have narrowing (irrespective of cause) of the gastrointestinal tract or have blind loops of the gastrointestinal tract or gastrointestinal obstruction

NCT01205126 (*Continued*)

	- Have any significant central nervous system (CNS) disorder or any disorder that predisposes the patient to respiratory depression - Have any condition wherein the risks of treatment with study drug may outweigh the potential benefits
Interventions	Hydromorphone hydrochloride (HCl), all patients will take 2 capsules (caps) twice daily for up to 36 days as follows: 1 cap containing 8 mg or 16 mg of hydromorphone HCL (H) + 1 cap of dummy placebo (DP) followed 12 hr later by 2 caps containing DP or 2 caps containing 24 mg or 32 mg H followed 12 hr later by 2 caps DP versus Oxycodone HCl CR, all patients will take 2 caps twice daily for up to 36 days as follows: 1 cap containing 10 mg, 20 mg or 40 mg oxycodone HCL CR (Oxy) + 1 cap of DP administered at 12 hour intervals or 1 cap containing 10 mg Oxy + 1 cap containing 20 mg Oxy administered at 12 hour intervals
Outcomes	Primary outcome measures: - Patient assessment of pain at its worst in the last 24 hours, included as an item in the Brief Pain Inventory (BPI) Short Form, where 0 = no pain and 10 = pain as bad as you can imagine. (Time frame: at endpoint (the last recorded value obtained up to the end of the study (Day 29 ± 1 day)) Secondary outcome measures: - Other assessments of pain severity and pain relief from the BPI (Short Form). (Time frame: from Day 1 (baseline or randomisation) to the last recorded value obtained up to the end of the study (Day 29 ± 1 day)) - Number of breakthrough pain medication doses taken (time frame: from Day 1 in the titration phase up through the end of the study (Day 29 ± 1 day)) - Number of patients with treatment emergent adverse events, serious adverse events and adverse events leading to discontinuation from the study (time frame: from Day 1 in the titration phase up through the end of the study (Day 29 ± 1 day))
Starting date	December 2009
Contact information	Location: China Sponsors, collaborators, investigators, study director: Johnson & Johnsopn Pharmaceutical Research & Development, L.L.C. Clinical Trial (no other contact information reported)
Notes	Target enrolment: N = 258 Study completion date: February 2011 Other study ID numbers: CR017437, 42801PA|3009

NCT01675622

Trial name or title	A Comparative Study of Immediate-Release Oxycodone Capsules Versus Immediate-Release Morphine Tablets for the Treatment of Chinese Patients With Cancer Pain
Methods	Randomised, parallel-group, double (triple?)-blind (patient, care-giver, investigator, outcome-assessor) controlled trial
Participants	Inclusion criteria: - Patients of either sex aged 18 to 80 years inclusive, with cancers of all types - Patients with moderate to severe cancer pain, whose pain intensity NRS $\geq$ 4 - Patients who can understand and are able to complete NRS and BPI assessment - Patients who have given written informed consent to participate in the study

	Exclusion criteria: - Patients who are pregnant, or lactating - Patients who are unable to manage their pain effectively with opioids - Patient who need ≥ 120mg morphine or equivalent for treatment of pain at time of study entry - Patients who are receiving chemotherapy, or still under the responsive period of chemotherapy (patients who are at the interval period of chemotherapy can be enrolled into study. That is to say, patients who completed chemotherapy for more than 2 weeks can enrolled, or patients has completed chemotherapy for at least one week could be enrolled at the discretion of the investigator) - Patients who have received radiotherapy for bony metastasis, patients receiving radiotherapy within the 4-week period before study entry (patient receiving radiotherapy for area other than pain area can be enrolled) , or patients who were scheduled to receive radiotherapy for pain area during study period - Patients are receiving or should receive anticonvulsive drugs or antidepressant drugs considered by investigator for the treatment of neuropathy pain - Patients are receiving or should receive any analgesic other than study medicine, including NSAIDs - Patients with other unstable disease, or with dysfunction of important organ - Patients with an ongoing infection, abscess or fever - Patient with serious abnormal liver or renal function (ALT, AST, creatinine, urea nitrogen) which is higher than 3 times upper limit - Paralytic or mechanical ileus - Persistent asthma, chronic obstructive diseases, and cor pulmonary - Intracranial neoplasms, and intracranial hypertension with central respiratory depression risk - Monoamine oxidase inhibitors (MAOIs) or same type drugs have been administered in last 2 weeks - Patients who are currently taking active treatment for epilepsy or arrhythmias - Patients with known sensitivity or record of specific or allergic reaction to oxycodone or morphine - Patients excluded by the contra-indications, adverse drug reaction (ADRs) and drug interactions of oxycodone or morphine as detailed in the data sheet, summary of product characteristics or investigator's brochure - Patients with a history of drug or alcohol abuse - Patients who participated in another clinical research study involving a new chemical entity within one month prior to study entry - Patients whose concomitant medication is likely to be changed within the study period, with the exception of treatment for opioid side effects - Patients who, in the opinion of the investigator, are unsuitable to participate in the study for any other reason not mentioned in the inclusion and exclusion criteria
Interventions	Oxycodone (5 mg, l0 mg and 20 mg capsules every 6 h, 5 to 8 days) versus morphine (tablets 10 mg and 20 mg, oral every 4 to 6 hours)
Outcomes	Primary outcome measures: - NRS (Numerical Rating Scale) score (time frame: 5 to 8 days). To compare the average for decrease of NRS score after double-blind treatment between the two treatment groups - The average dose of study medicine used during double blind treatment period (time frame: 5 to 8 days). To compare the average dose of study medicine used during double-blind treatment period between the two treatment groups Secondary outcome measures: - BPI (Brief pain inventory) (time frame: 19 to 22 days). To compare BPI score at baseline, after completion of double-blind treatment and open-label treatment to baseline between the two treatment groups - Times and frequency of breakthrough pain and the total dose of rescue medicine for breakthrough pain (time frame: 19 to 22 days). To compare the times and frequency of breakthrough pain and the total dose of rescue medicine for breakthrough pain during double-blind phase between the two treatment groups

NCT01675622 (*Continued*)

	- Patient assessments of satisfaction for pain management (time frame: 19 to 22 days). To compare patient assessments of satisfaction for pain management between the two treatment groups at the end of double-blind treatment and the open-label treatment period - Average time for titration (time frame: 1 to 3 days). To compare the average time for titration between the two treatment groups
Starting date	December 2010
Contact information	Location: China Sponsors, collaborators: Mundipharma Principal investigator: Shiying Yu, Wuhan Tong Ji Hospital
Notes	Target enrolment: N = 240 Study completion date: July 2012 Other study ID numbers: OXYC10-CN-303

NCT01809106

Trial name or title	RCT Comparing the Analgesic Efficacy of 4 Therapeutic Strategies Based on 4 Different Major Opioids (Fentanyl, Oxycodone, Buprenorphine vs Morphine) in Cancer Patients With Moderate/Severe Pain, at the Moment of Starting 3rd Step of WHO Analgesic Ladder
Methods	Randomised (parallel? cross-over?), open-label controlled trial
Participants	Inclusion criteria: - Patients with diagnostic (histological or cytological) evidence of locally advanced or metastatic solid tumour - with average pain intensity $\geq$ 4, measured with NRS and related to the last 24 hours, due to the cancer, requiring for the first time an analgesic treatment with third step WHO opioids - life expectancy > one month - 'strong' opioid naïve - eligible to take any of the medications under evaluation, by transdermal system (TDS) or by mouth - age $\geq$ 18 years Exclusion criteria: - Patients recruited in other researches that conflict or may confound the conduction and results of the present study - lack of informed consent - with presence of other diseases, including psychiatric or mental illness, severe senile or other form of dementia that can interfere with participation and compliance with the study protocol or can contra-indicate the use of the investigational drugs - with presence of co-morbidities, which could create potentially dangerous drug interactions with opioids (e.g., use of macrolide antibiotics or antifungal) - any kind of contraindications to the use of opioid drugs - with a known story, past or current, of drugs abuse or addiction - use of drugs which present a combination of opioids and other molecule (such as NSAIDs, paracetamol, naloxone) - who cannot guarantee regular follow-up visits for logistic or geographic reasons - need of starting third step treatment in an 'emergency clinical situation' that does not allow the correct procedures of randomisation

NCT01809106 (*Continued*)

	- diagnosis of primary brain tumour or leukaemia - diagnosis of chronic renal failure - patients with antalgic radiotherapy or radio-metabolic therapy in progress or completed less than 14 days before study - patients starting a first line chemotherapy simultaneously to the beginning of the study - other types of analgesic treatments, including local-regional anesthetic techniques or neurosurgical or ablative methods
Interventions	Morphine (60 mg/24 hours) versus oxycodone (40 mg/24 hours) versus buprenorphine (35 µg/hour) versus fentanyl (25 µg/hour)
Outcomes	Primary outcome measures: - Proportion of non-responder (NR) patients (time frame: 28 days) - Evaluation of the proportion of NR patients. NRs correspond to the subjects who do not report any analgesic effects, with a pain intensity difference (PID) from visit 6 and visit 1 $\leq$ 0%, (using a 0 to 10 NRS). It includes the situations of average pain intensity 'stable' or 'worsened' at day 28 compared with baseline values Secondary outcome measures: - Proportion of full responders (FR) (time frame: 28 days) - Evaluation of the proportion of subjects who report full analgesia (FR). FR is operationally defined as a patient with a PID $\geq$ 30% from visit 6 and visit 1 (NRS 0 to 10) Other outcome measures: - The opioid escalation index (time frame: 28 days) - The proportion of subjects with an increase of opioid daily dose > 5% compared with the basal dosage (OEI%)
Starting date	April 2011
Contact information	Location: Italy Sponsors, collaborators: Mario Negri Institute for Pharmacological Research Principal investigator: Oscar Corli, MD. Mario Negri Institute of Pharmacological Research - IRCCS Contact: oscar.corli@marionegri.it; anna.roberto@email.it
Notes	Target enrolment: N = 600 Study completion date: April 2014 Other study ID numbers: None reported

NCT02084355

Trial name or title	Efficacy and Safety of Opioid Rotation Compared With Opioid Dose Escalation in Patients With Moderate to Severe Cancer Pain - Open Label, Randomized, Prospective Study
Methods	Open-label, randomised, prospective study
Participants	Inclusion criteria: - age > 18 years - patients who are being treated with one of strong opioids including oral oxycodone, oral hydromorphone,

NCT02084355 (*Continued*)

	or fentanyl patch with range from 60 mg to 200 mg of oral morphine equivalent daily dose (MEDD) - moderate to severe cancer pain (numeric rating scale more than 3) at screening - patients without uncontrolled adverse effects associated with currently applied opioid Exclusion criteria: - previous opioid rotation - unable to take oral medication - life expectancy less than a month - newly started chemotherapy or radiotherapy within past 2 weeks of screening - serum aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase > 2.5 times upper normal limit - serum total bilirubin or creatinine > 1.5 times of upper normal limit
Interventions	Opioid rotation: Patients who are randomised to opioid rotation are treated with strong opioid other than currently used strong opioid (reduce the dose by 25% to 50% to allow for incomplete cross-tolerance between different opioids): Oral oxycodone: convert to oral hydromorphone or fentanyl patch Oral hydromorphone: convert to oral oxycodone or fentanyl patch Fentanyl patch: convert to oral oxycodone or oral hydromorphone versus opioid dose escalation: Patients who are randomised to opioid dose escalation will be treated cancer pain by escalation dose of same strong opioid: Oral oxycodone: maintain oral oxycodone and titrate the dose Oral hydromorphone: maintain oral hydromorphone and titrate the dose Fentanyl patch: maintain fentanyl patch and titrate the dose
Outcomes	Primary outcome measures: The rate of successful pain control defined as a 30% or 2-point reduction in the numeric rating scale (time frame: 18 months). (Designated as safety issue: Yes)
Starting date	April 2014
Contact information	Location: Republic of Korea Sponsors, collaborators: Gyeongsang National University Hospital Principal investigator/contact: Se-Il Go, M.D., tel@ +82 55 750 9454 ext 9454, e-mail: gose1@hanmail.net
Notes	Target enrolment: N = 136 Study completion date: January 2016 Other study ID numbers: GNUH-2013-07-014

UMIN000011756

Trial name or title	Randomized study of fentanyl citrate versus Oxycodone Hydrochloride Hydrate in patients with unresectable advanced pancreatic cancer (FRONTIER)
Methods	Randomised, single arm (?), phase III, open trial

UMIN000011756 (*Continued*)

Participants	Inclusion criteria: - Aged 20 to < 100 years - unresectable advanced pancreatic cancer - ≥ 15 to 25 mg oxycodone hydrochloride hydrate per day required for cancer pain Exclusion criteria: - Serious liver, kidney, cardiac disorders - pulmonary impairment - nervous system and psychic disorders
Interventions	Oxycodone hydrochloride hydrate: 10 mg every 12 hours, versus Transdermal fentanyl citrate: 1 mg once a day
Outcomes	Primary outcome measures: The rates of gastrointestinal disorders events in four weeks Secondary outcome measures: Quality of life, rates of opioid rotation, pain score, time until stable pain control, overall survival time, adverse events
Starting date	27 March 2014
Contact information	Location: Japan Sponsors, collaborators: National Cancer Center Hospital East; Welfare labor science research cost (MHLW (Japan)) Principal investigator/contact: Minori Odanaka, Clinical Trial Support Office, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan Tel: +81-3-3547-5201, e-mails: minochant23@yahoo.co.jp; modanaka@ncc.go.jp
Notes	Target enrolment: N = 80 Study completion date: Not reported Other study ID numbers: None reported

DATA AND ANALYSES

Comparison 1. Pain

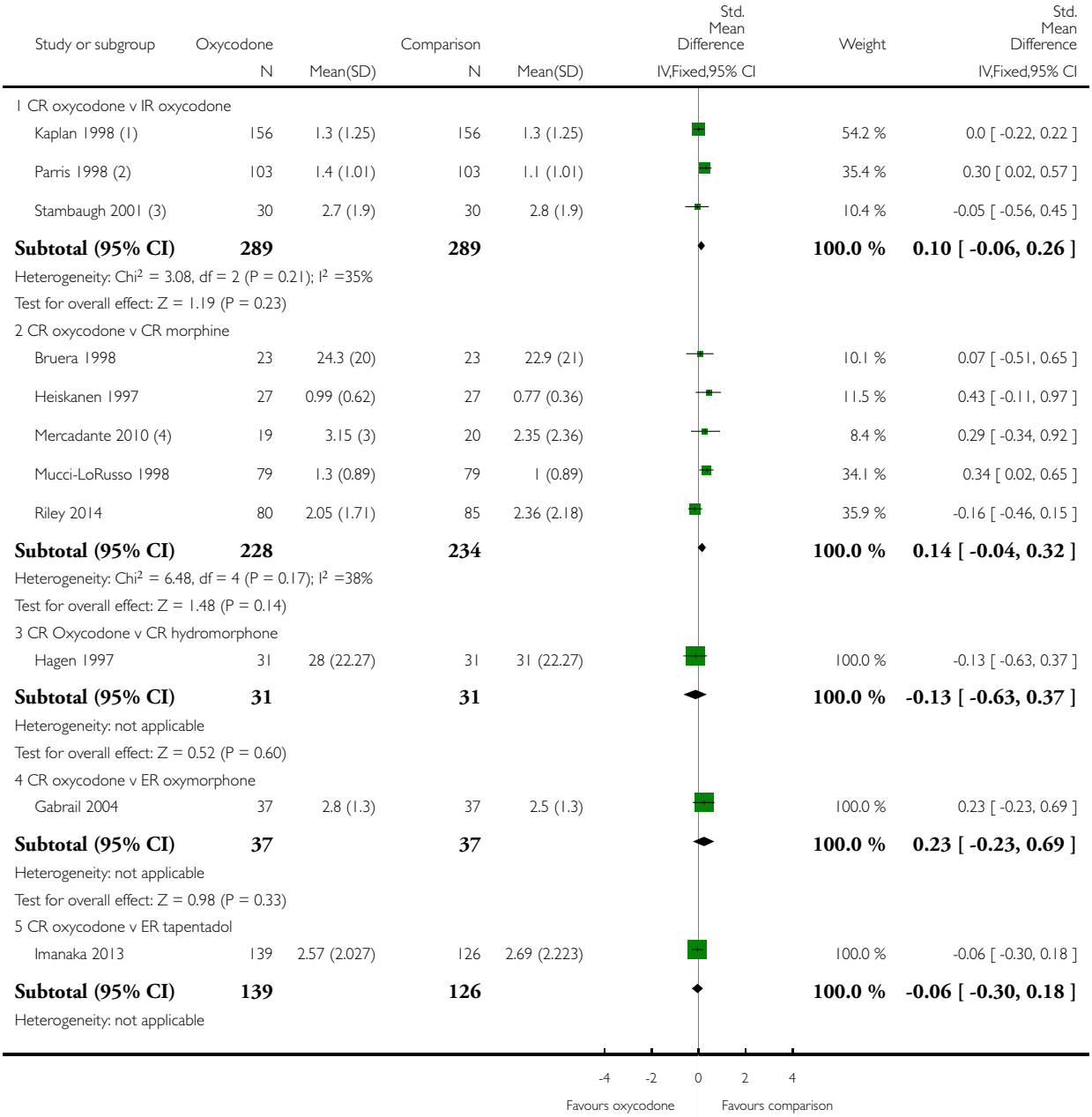
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain intensity	12		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 CR oxycodone v IR oxycodone	3	578	Std. Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.06, 0.26]
1.2 CR oxycodone v CR morphine	5	462	Std. Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.04, 0.32]
1.3 CR Oxycodone v CR hydromorphone	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.63, 0.37]
1.4 CR oxycodone v ER oxymorphone	1	74	Std. Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.23, 0.69]
1.5 CR oxycodone v ER tapentadol	1	265	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.30, 0.18]
1.6 IR oxycodone v IR morphine	1	38	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.79, 0.49]

Analysis 1.1. Comparison 1 Pain, Outcome 1 Pain intensity.

Review: Oxycodone for cancer-related pain

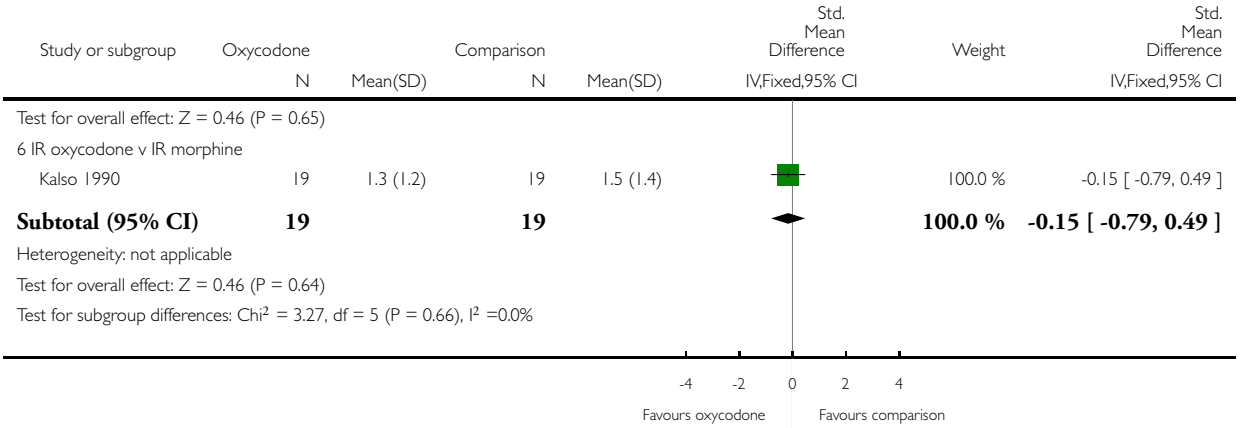
Comparison: 1 Pain

Outcome: 1 Pain intensity



(*Continued* . . .)

(. . . *Continued*)



(1) Please note that in comparison 1.1.1, CR oxycodone is input as the 'oxycodone' group and IR oxycodone is input as the 'comparison' group.

(2) Please note that in comparison 1.1.1, CR oxycodone is input as the 'oxycodone' group and IR oxycodone is input as the 'comparison' group.

(3) Please note that in comparison 1.1.1, CR oxycodone is input as the 'oxycodone' group and IR oxycodone is input as the 'comparison' group.

(4) Week 4 data

ADDITIONAL TABLES

Table 1. Summary of findings table

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oxycodone	comparison		
CR oxycodone versus immediate-release (IR) oxycodone: pain intensity										
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313[2]	313[2]	SMD 0.1 (95% CI -0.06 to 0.26)	LOW
CR oxycodone versus IR oxycodone: adverse events										
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313[2]	313[2]	No or only very minor	LOW

Table 1. Summary of findings table (*Continued*)

									differences between the treatment groups	
CR oxycodone versus IR oxycodone: treatment acceptability										
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	289[2]	289[2]	No difference between the treatment groups	LOW
CR oxycodone versus CR morphine: pain intensity										
5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	228[3]	234[3]	SMD 0.14 (95% CI -0.04 to 0.32)	LOW
CR oxycodone versus CR morphine: adverse events										
5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	229[3]	221[3]	No or only very minor differences between the treatment groups	LOW
CR oxycodone versus CR morphine: treatment acceptability										
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	129[3]	129[3]	Two studies found no differences, whereas one study found superior acceptability of morphine	VERY LOW
CR oxycodone versus CR hydromorphone: pain intensity										

Table 1. Summary of findings table (*Continued*)

1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	31[5]	31[5]	No difference between the treatment groups	VERY LOW
CR oxycodone versus CR hydromorphone: adverse events										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	31[5]	31[5]	No differences between the treatment groups, apart from more drowsiness during oxycodone treatment	VERY LOW
CR oxycodone versus CR hydromorphone: treatment acceptability										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	31[5]	31[5]	No difference between the treatment groups	VERY LOW
CR oxycodone versus ER oxymorphone: pain intensity										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	37[5]	37[5]	No difference between the treatment groups	VERY LOW
CR oxycodone versus ER oxymorphone: adverse events										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	37[5]	37[5]	No differences between the treatment groups	VERY LOW
CR oxycodone versus ER oxymorphone: treatment acceptability										

Table 1. Summary of findings table (*Continued*)

1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	37[5]	37[5]	78.3% rated oxycodone and 86.4% rated oxymorphone, excellent, very good or good	VERY LOW
CR oxycodone versus ER oxymorphone: quality of life										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	37[5]	37[5]	No differences between the treatment groups	VERY LOW
CR oxycodone versus ER tapentadol: pain intensity										
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	139	126	No difference between the treatment groups	VERY LOW
CR oxycodone versus ER tapendatol: adverse events										
1	randomised trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	139	126	No apparent differences between the treatment groups	VERY LOW
IV oxycodone versus rectal oxycodone: pain intensity										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	12[5]	12[5]	Faster onset of pain relief with IV oxycodone, longer duration of	VERY LOW

Table 1. Summary of findings table (*Continued*)

									pain relief with rectal oxycodone	
IV oxycodone versus rectal oxycodone: adverse events										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	12[5]	12[5]	No differences between the treatment groups	VERY LOW
IV oxycodone followed by IR oxycodone versus IV morphine followed by IR morphine: pain intensity										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	19[5]	19[5]	30% more IV oxycodone (than IV morphine) and 25% less IR oxycodone (than IR morphine) needed to achieve equal analgesia	VERY LOW
IV oxycodone followed by IR oxycodone versus IV morphine followed by IR morphine: adverse events										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	19[5]	19[5]	No differences between the treatment groups, apart from more nausea with IR morphine treatment	VERY LOW

Table 1. Summary of findings table (*Continued*)

IV oxycodone followed by IR oxycodone versus IV morphine followed by IR morphine: treatment preference										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	19[5]	19[5]	No differences between the treatment groups	VERY LOW
IM oxycodone versus oral oxycodone: pain intensity										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	13[5]	13[5]	Oral oxcodone was 0.57 (95% CI 0.22 to 1.84) times as potent as IM oxycodone for pain relief and 0.78 (95% CI 0.3 to 8.82) times as potent for change in pain intensity	VERY LOW
IM oxycodone versus IM morphine: pain intensity										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	28[5]	28[5]	IM oxcodone was 0.74 (95% CI 0.36 to 1.2) times as potent as IM morphine for pain relief and 0.68 (95% CI	VERY LOW

Table 1. Summary of findings table (*Continued*)

									0.32 to 1.07) times as potent for change in pain intensity	
IM oxycodone versus IM codeine: pain intensity										
1	randomised cross-over trial	very serious[1]	no serious inconsistency	no serious indirectness	imprecision[4]	none	26[5]	26[5]	IM oxcodone was 10.72 (95% CI not reported) times as potent as IM codeine for pain relief and 8.44 (95% CI 2.13 to 44.69) times as potent for change in pain intensity	VERY LOW

Please note: CR = controlled release, IR = immediate release, ER = extended release, IV = intravenous, IM = intramuscular.

[1] The quality of the evidence provided by the included studies was compromised by under-reporting, lack of blinding and/or missing data.

[2] One of the included studies was a cross-over trial with 30 patients. These 30 patients are included in the totals for both CR oxycodone and IR oxycodone.

[3] Two of the included studies were cross-over trials with a total of 50 patients. These 50 patients are included in the totals for both CR oxycodone and CR morphine.

[4] Low numbers of patients.

[5] The included study was a cross-over trial. The total number of patients are listed in the totals for both CR oxycodone and CR hydromorphone.

Table 2. Controlled-release (CR) oxycodone versus immediate-release (IR) oxycodone: adverse events

Comparison	CR oxycodone versus IR oxycodone							
Study	Kaplan 1998		Parris 1998*		Salzman 1999		Stambaugh 2001	
	CR	IR	CR	IR	CR	IR	CR	IR
Any adverse events			38/54-55	38/54-55			10/30	10/30
Total adverse events	109	186	138	142				
Abdominal pain			3/54-55	1/54-55				
Anxiety	0/78	4/82						
Asthenia	3/78	8/82			2/24	1/24	2/30	2/30
Confusion			0/54-55	2/54-55	3/24	2/24		
Constipation	9/78	17/82	12/54-55	10/54-55	4/24	9/24	1/30	1/30
Dizziness, lightheadedness	5/78	11/82	8/54-55	10/54-55	2/24	0/24	3/30	3/30
Drowsiness, somnolence	14/78	17/82	13/54-55	12/54-55	9/24	7/24	3/30	2/30
Dry mouth	3/78	5/82	4/54-55	3/54-55	3/24	1/24	1/30	1/30
Headache	0/78	6/82	7/54-55	3/54-55	1/24	1/24		
Insomnia	2/78	4/82	3/54-55	1/54-55				
Nausea	14/78	21/82	11/54-55	13/54-55	7/24	5/24	4/30	3/30
Nervousness	3/78	5/82			2/24	4/24	0/30	1/30
Postural hypotension					5/24	4/24		
Pruritus	2/78	4/82	7/54-55	5/54-55	4/24	0/24	1/30	2/30
Sweating	4/78	3/82	1/54-55	5/54-55			2/30	1/30

Table 2. Controlled-release (CR) oxycodone versus immediate-release (IR) oxycodone: adverse events (*Continued*)

Vomiting	8/78	14/82	5/54-55	11/54-55	5/24	3/24	2/30	0/30
Discontinuation due to AE	6/78	10/82	4/54-55	7/54-55	1/24	2/24		

*Total number of patients for safety evaluation = 109. Not clear which group had 55 and 54 patients, respectively.

Table 3. Controlled-release (CR) oxycodone versus CR morphine: adverse events

Comparison	CR oxycodone versus CR morphine											
Study	Bruera 1998		Heiskanen 1997		Lauretti 2003		Mercadante 2010*		Mucci-LoRusso 1998		Riley 2014	
	Oxy	Mor	Oxy	Mor	Oxy	Mor	Oxy	Mor	Oxy	Mor	Oxy	Mor
Any adverse events									40/48	39/52		
Abnormal dreams											3/81	1/72
Anorexia, appetite loss			0/27	1/27	14/22	13/22					1/81	0/72
Chills			1/27	0/27								
Confusion - serious							0.37 (0.49)	0.25 (0.44)			7/81 3/81	2/72 0/72
Constipation - serious			18/27	14/27	4/22	5/22	0.63 (0.68)	0.7 (0.92)	10/48	10/52	18/81 2/81	24/72 5/72
Decreased mobility											0/81	2/72

Table 3. Controlled-release (CR) oxycodone versus CR morphine: adverse events (*Continued*)

Depression			1/27	0/27								
Diarrhoea			2/27	2/27								
Dizziness, lightheadedness			6/27	6/27					4/48	7/52	3/81	2/72
Double vision											0/81	1/72
Drowsiness, somnolence - serious (with hallucinations)					7/22	11/22	0.37 (0.6)	0.35 (0.59)	7/48	10/52	12/81 1/81	13/72 0/72
Drunken feeling			1/27	1/27								
Dry mouth			12/27	15/27	3/22	2/22	0.63 (0.68)	0.6 (0.68)	1/48	7/52	3/81	2/72
Dyspnoea			2/27	2/27	0/22	0/22						
Extrasystoles			1/27	0/27								
Faecal incontinence			1/27	1/27								
Fall											0/81	3/72
Feeling abnormal											0/81	1/72

Table 3. Controlled-release (CR) oxycodone versus CR morphine: adverse events (*Continued*)

Flatus			0/27	1/27								
Hallucinations					0/22	0/22			0/48	2/52	3/81	4/72
Hollow feeling			1/27	0/27								
Lethargy											1/81	0/72
Memory impairment											1/81	1/72
Muscle twitches			1/27	1/27							0/81	2/72
Nausea - serious (with vomiting)	12.3	13.9	14/27	16/27	1/22	8/22	0.84 (0.9)	0.6 (0.75)	6/48	8/52	10/81 1/81	6/72 0/72
Nightmares			0/27	3/27							2/81	0/72
Pain											0/81	1/72
Parasthesia											1/81	0/72
Pruritus			10/27	7/27	1/22	1/22			4/48	5/52	3/81	2/72
Sedation	21.4	25	16/27	18/27								
Sensation of empty head					1/22	0/11						
Slow speech											1/81	0/72

Table 3. Controlled-release (CR) oxycodone versus CR morphine: adverse events (*Continued*)

Sweating, hyperhidrosis			12/27	9/27							2/81	0/72
Serious toxicity secondary to infection											1/81	0/72
Urinary hesitation											0/81	1/72
Visual impairment											1/81	0/72
Vomiting			5/27	10/27	0/22	7/22			6/48	5/52	9/81	4/72
Discontinuation due to AE									3/48	6/52		
Unexpected serious adverse events											2/81	7/72

*Mean (SD) ratings (out of 3) experienced during week 4.

Table 4. Single-study comparisons: adverse events

Comparison	CR oxycodone versus CR hydromorphone		CR oxycodone versus ER oxymorphone		CR oxycodone versus ER tapentadol		IV oxycodone versus rectal oxycodone		IV oxycodone followed by IR oxycodone versus IV morphine followed by IR morphine			
Study	Hagen 1997		Gabrail 2004		Imanaka 2013		Leow 1995**		Kalso 1990***			
	Oxy	Hyd	Oxyco	Oxymo	Oxy	Tap	IV	Rectal	IV oxy	IR oxy	IV mor	IR mor

Table 4. Single-study comparisons: adverse events (*Continued*)

Any adverse events					155/172	147/168						
Total adverse events							82	94				
Anorexia, appetite loss					24/172	23/168						
Confusion									0/19	1/19	0/19	1/19
Constipation			19/41	21/43	64/172	51/168			6/19	6/19	8/19	8/19
Delirium					6/172	10/168						
Diarrhoea					19/172	11/168						
Dizziness or lightheadedness			9/41	7/43			0.54 (0.74)	0.71 (0.9)				
Drowsiness, somnolence	28/31	19/31			36/172	29/168	0.68 (0.81)	0.79 (0.93)	7/19	4/19	4/19	5/19
Hallucinations	0/31	2/31							0/19	0/19	2/19	3/19
Insomnia					11/172	9/168						
Nausea	15 (3)*	13 (3)*	15/41	17/43	61/172	48/168	0.02 (0.15)	0.12 (0.45)	7/19	7/19	7/19	12/19
Pruritus			8/41	13/43			0.05 (0.21)	0.05 (0.21)	3/19	1/19	3/19	2/19

Table 4. Single-study comparisons: adverse events (*Continued*)

Sedation	24 (4)*	18 (3)*	13/41	18/43					12/19	13/19	12/19	14/19
Sweating			9/41	12/43			0.04 (0.19)	0.07 (0.3)	4/19	2/19	1/19	1/19
Urinary retention									1/19	1/19	2/19	0/19
Vomiting			7/41	5/43	41/172	42/168	0.01 (0.11)	0.01 (0.11)				
Discontinuation due to AE					29/172	22/168						

*Mean (SE) VAS across all days.
**Mean (SD) ratings (out of 3) experienced during the 24 hours of drug administration, apart from the total number of adverse events which is read from the authors' Figure 3.
**The measure is the sum of positive responses after each study period: moderate = 1, severe = 2.

APPENDICES

Appendix 1. MEDLINE search strategy

CENTRAL (Cochrane Library)
#1 MeSH descriptor: [Oxycodone] explode all trees
#2 (ox?codon* or oxycontin or oxycodeinon or oxycone or oxycdn or ox?conum or oxydose or oxyfast or oxygesic or oxynorm or oxynormoro or oxyrapid):ti,ab,kw (Word variations have been searched)
#3 (dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon):ti,ab,kw (Word variations have been searched)
#4 (endocet or endocodone or endone or eu?odal or eubine):ti,ab,kw (Word variations have been searched)
#5 ("m oxy" or oxecta or oxydihydrocodeinonum or pancodine or pavinal or percocet or percolone or proladone):ti,ab,kw (Word variations have been searched)
#6 (remoxy or roxicet or rox?codone or roxilox):ti,ab,kw (Word variations have been searched)
#7 (supeudol or thecodinum or theocodin or tylox):ti,ab,kw (Word variations have been searched)
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Neoplasms] explode all trees
#10 (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*):ti,ab,kw (Word variations have been searched)
#11 #9 or #10
#12 #8 and #11
MEDLINE and MEDLINE In-Process (Ovid)

1 Oxycodone/
2 (ox?codon$ or oxycontin or oxycodeinon or oxycone or oxycdn or ox?conum or oxydose or oxyfast or oxygesic or oxynorm or oxynormoro or oxyrapid).tw.
3 (dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon).tw.
4 (endocet or endocodone or endone or eu?odal or eubine).tw.
5 ("m oxy" or oxecta or oxydihydrocodeinonum or pancodine or pavinal or percocet or percolone or proladone).tw.
6 (remoxy or roxicet or rox?codone or roxilox).tw.
7 (supeudol or thecodinum or theocodin or tylox).tw.
8 or/1-7
9 exp Neoplasms/
10 (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or nonhodgkin$ or adenocarcinoma$ or leuk?emia$1 or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or oncolog$).tw.
11 or/9-10
12 8 and 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 drug therapy.fs.
18 randomly.ab.
19 trial.ab.
20 or/13-19
21 exp animals/ not humans.sh.
22 20 not 21
23 12 and 22

EMBASE (Ovid)

1 Oxycodone/
2 (ox?codon$ or oxycontin or oxycodeinon or oxycone or oxycdn or ox?conum or oxydose or oxyfast or oxygesic or oxynorm or oxynormoro or oxyrapid).tw.
3 (dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon).tw.
4 (endocet or endocodone or endone or eu?odal or eubine).tw.
5 ("m oxy" or oxecta or oxydihydrocodeinonum or pancodine or pavinal or percocet or percolone or proladone).tw.
6 (remoxy or roxicet or rox?codone or roxilox).tw.
7 (supeudol or thecodinum or theocodin or tylox).tw.
8 or/1-7
9 exp Neoplasms/
10 (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or nonhodgkin$ or adenocarcinoma$ or leuk?emia$1 or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or oncolog$).tw.
11 or/9-10
12 8 and 11
13 random$.tw.
14 factorial$.tw.
15 crossover$.tw.
16 cross over$.tw.
17 cross-over$.tw.
18 placebo$.tw.
19 (doubl$ adj blind$).tw.
20 (singl$ adj blind$).tw.
21 assign$.tw.
22 allocat$.tw.
23 volunteer$.tw.
24 Crossover Procedure/
25 double-blind procedure.tw.

26 Randomized Controlled Trial/
27 Single Blind Procedure/
28 or/13-27
29 (animal/ or nonhuman/) not human/
30 28 not 29
31 12 and 30

Web of Science (ISI) SSCI and SCI

#22 #21 AND #9
#21 #20 OR #17 OR #16 OR #15 OR #14 OR #11 OR #10
#20 #19 AND #18
#19 TS=random* OR TI=random*
#18 TS=(allocate* OR assign*) OR TI=(allocate* OR assign*)
#17 TS=crossover* OR TI=crossover*
#16 TS=(mask* OR blind*) OR TI=(mask* OR blind*)
#15 TS=(singl* OR Doubl* OR Tripl* OR Trebl*) OR TI=(singl* OR Doubl* OR Tripl* OR Trebl*)
#14 #13 AND #12
#13 TS=trial* OR TI=trial*
#12 TI=clin* OR TS=clin*
#11 TI=randomi* OR TS=randomi*
#10 TS=Randomized clinical trial* OR TI=Randomized clinical trial*
#9 #8 AND #7
#8 Topic=((cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*))
#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
#6 Topic=((supeudol or thecodinum or theocodin or tylox))
#5 Topic=((remoxy or roxicet or rox?codone or roxilox))
#4 Topic=((“m oxy” or oxecta or oxydihydrocodeinonum or pancodine or pavinal or percocet or percolone or proladone))
#3 Topic=((endocet or endocodone or endone or eu?odal or eubine))
#2 Topic=((dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon))
#1 Topic=((ox?codon* or oxycontin or oxycodeinon or oxycone or oxycdn or ox?conum or oxydose or oxyfast or oxygesic or oxynorm or oxynormoro or oxyrapid))

BIOSIS (ISI)

#21 #20 AND #19 AND #12
#20 Topic=(((cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*)))
#19 #18 OR #17 OR #16 OR #15 OR #14 OR #13
#18 Topic=(((supeudol or thecodinum or theocodin or tylox)))
#17 Topic=(((remoxy or roxicet or rox?codone or roxilox)))
#16 Topic=(((“m oxy” or oxecta or oxydihydrocodeinonum or pancodine or pavinal or percocet or percolone or proladone)))
#15 Topic=(((endocet or endocodone or endone or eu?odal or eubine)))
#14 Topic=(((dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon)))
#13 Topic=(((ox?codon* or oxycontin or oxycodeinon or oxycone or oxycdn or ox?conum or oxydose or oxyfast or oxygesic or oxynorm or oxynormoro or oxyrapid)))
#12 #11 OR #8 OR #7 OR #6 OR #5 OR #2 OR #1
#11 #10 AND #9
#10 DS=random* OR TS=random* OR TI=random*
#9 DS=(allocate* OR assign*) OR TS=(allocate* OR assign*) OR TI=(allocate* OR assign*)
#8 DS=crossover* OR TS=crossover* OR TI=crossover*
#7 DS=(mask* OR blind*) OR TS=(mask* OR blind*) OR TI=(mask* OR blind*)
#6 DS=(singl* OR Doubl* OR Tripl* OR Trebl*) OR TS=(singl* OR Doubl* OR Tripl* OR Trebl*) OR TI=(singl* OR Doubl* OR Tripl* OR Trebl*)
#5 #4 AND #3
#4 DS=trial* OR TS=trial* OR TI=trial*

#3 DS=clin* OR TI=clin* OR TS=clin*
#2 DS=randomi* OR TI=randomi* OR TS=randomi*
#1 MQ=Randomized clinical trial* OR DS=Randomized clinical trial* OR TS=Randomized clinical trial* OR TI=Randomized clinical trial*

PsycINFO (Ovid)

1 (ox?codon$ or oxycontin or oxycodeinon or oxycone or oxycdn or ox?conum or oxydose or oxyfast or oxygesic or oxynorm or oxynormoro or oxyrapid).tw.
2 (dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon).tw.
3 (endocet or endocodone or endone or eu?odal or eubine).tw.
4 ("m oxy" or oxecta or oxydihydrocodeinonum or pancodine or pavinal or percocet or percolone or proladone).tw.
5 (remoxy or roxicet or rox?codone or roxilox).tw.
6 (supeudol or thecodinum or theocodin or tylox).tw.
7 exp Neoplasms/
8 (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or nonhodgkin$ or adenocarcinoma$ or leuk?emia$1 or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or oncolog$).tw.
9 or/7-8
10 or/1-6
11 9 and 10
12 clinical trials/
13 (randomis* or randomiz*).tw.
14 (random$ adj3 (allocat$ or assign$)).tw.
15 ((clinic$ or control$) adj trial$).tw.
16 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
17 (crossover$ or "cross over$").tw.
18 random sampling/
19 Experiment Controls/
20 Placebo/
21 placebo$.tw.
22 exp program evaluation/
23 treatment effectiveness evaluation/
24 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
25 or/12-24
26 11 and 25

PubMed

(((Oxycodone[MeSH Terms]) OR ((ox?codon* OR oxycontin OR oxycodeinon OR oxycone OR oxycdn OR ox?conum OR oxydose OR oxyfast OR oxygesic OR oxynorm OR oxynormoro OR oxyrapid)) OR ((dazidox OR dihydrohydroxycodeinone OR dihydrone OR dinarkon)) OR ((endocet OR endocodone OR endone OR eu?odal OR eubine)) OR (("m oxy" OR oxecta OR oxydihydrocodeinonum OR pancodine OR pavinal OR percocet OR percolone OR proladone)) OR ((remoxy OR roxicet OR rox?codone OR roxilox)) OR ((supeudol OR thecodinum OR theocodin OR tylox))) AND and AND ((Neoplasms[MeSH Terms]) OR ((cancer* OR neoplas* OR tumo* OR carcinoma* OR hodgkin* OR nonhodgkin* OR adenocarcinoma* OR leuk?emia*1 OR metasta* OR malignan* OR lymphoma* OR sarcoma* OR melanoma* OR myeloma* OR oncolog*)))) AND and AND (((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type]) OR (randomized[Title/Abstract]) OR (placebo[Title/Abstract]) OR (drug therapy[Title/Abstract]) OR (randomly[Title/Abstract]) OR (trial[Title/Abstract]) OR (groups[Title/Abstract])) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms]))

HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 2, 2015

Date	Event	Description
22 February 2013	New citation required and major changes	This protocol has been significantly updated by new authors. See Published notes.
11 February 2010	New citation required and major changes	This protocol was originally published in Issue 4, 2002. As the authors were unable to commit time to the completion of the full review it was then withdrawn in January 2009. The original authors are now able to work on completing the full review and plan to do so by the end of 2010
13 January 2009	New citation required and major changes	Withdrawn: the review group was unable to maintain contact with the contact author. New authors are being sought to take over this protocol, please contact the PaPaS Review Group if you are interested in working on this review title
22 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MSH and MIB conceived and designed the review and wrote the protocol. SA devised and undertook the search strategy. MSH, NB, and JSH screened the search results and performed the data extraction and 'risk of bias' assessment of the included studies. MSH devised and performed the analysis strategy, and wrote the first draft of the full review. MIB interpreted the results and wrote the 'Authors conclusions' section. All the authors approved the final version of the review.

DECLARATIONS OF INTEREST

MSH: none known; MIB: none known; SA: none known; NB: none known; JSH: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the risk of bias assessments, we also included an item that captured whether data were available for both time periods in cross-over trials, in order to make explicit this potential source of bias.

NOTES

This protocol was originally published in Issue 4, 2002. As the authors were unable to commit time to the completion of the full review it was then withdrawn in January 2009. The original authors intended to publish in 2010 (Reid 2010) but experienced further delays. The current author team has completed the full review.